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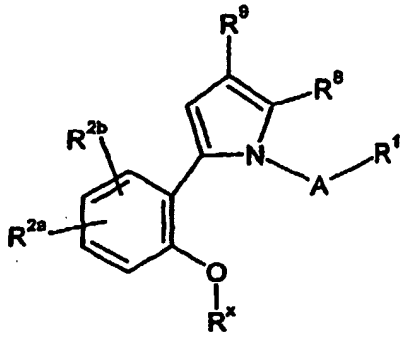
(54) Title: PYRROLE COMPOUNDS FOR THE TREATMENT OF PROSTAGLANDIN MEDIATED DISEASES



(I)

(57) Abstract: Compounds of formula (I) or a pharmaceutically acceptable derivative thereof: wherein A, R^1, R^{2a}, R^{2b}, R^x, R^8, and R^9 are as defined in the specification, a process for the preparation of such compounds, pharmaceutical compositions comprising such compounds and the use of such compounds in medicine, in particular their use in the treatment of prostaglandin mediated diseases such as pain, inflammatory, immunological, bone, neurodegenerative or renal disorder.

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PYRROLE COMPOUNDS FOR THE TREATMENT OF PROSTAGLANDIN MEDIATED DISEASES

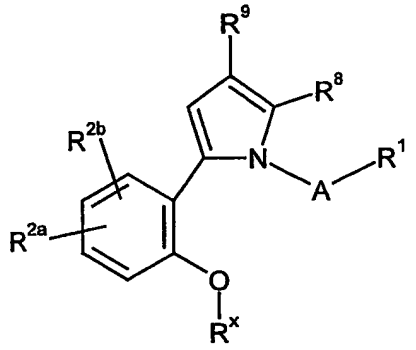
This invention relates to pyrrole compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, in particular their use in the treatment of prostaglandin mediated diseases.

The EP_1 receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE_2. PGE_2 also has affinity for the other EP receptors (types EP_2, EP_3 and EP_4). The EP_1 receptor is associated with smooth muscle contraction, pain (in particular inflammatory, neuropathic and visceral), inflammation, allergic activities, renal regulation and gastric or enteric mucus secretion. We have now found a novel group of compounds which bind with high affinity to the EP_1 receptor.

A number of review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids; From Biotechnology to Therapeutic Applications,* Folco, Samuelsson, Maclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and Journal of Lipid Mediators and Cell Signalling, 1996, 14, 83-87 and *Prostanoid Receptors, Structure, Properties and Function,* S Narumiya et al, Physiological Reviews 1999, 79(4), 1193-126. An article from *The British Journal of Pharmacology,*1994, 112, 735- 740 suggests that Prostaglandin E_2 (PGE_2) exerts allodynia through the EP_1 receptor subtype and hyperalgesia through EP_2 and EP_3 receptors in the mouse spinal cord. Furthermore an article from *The Journal of Clinical Investigation*, 2001, 107 (3), 325 shows that in the EP_1 knock-out mouse pain-sensitivity responses are reduced by approximately 50%. Two papers from *Anesthesia and Analgesia* have shown that (2001, 93, 1012-7) an EP_1 receptor antagonist (ONO-8711) reduces hyperalgesia and allodynia in a rat model of chronic constriction injury, and that (2001, 92, 233-238) the same antagonist inhibits mechanical hyperalgesia in a rodent model of post-operative pain. S. Sarkar *et al* in *Gastroenterology*, 2003, 124(1), 18-25 demonstrate the efficacy of EP_1 receptor antagonists in the treatment of visceral pain in a human model of hypersensitivity. Thus, selective prostaglandin ligands, agonists or antagonists, depending on which prostaglandin E receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug, and in addition, inhibit hormone-induced uterine contractions and have anti-cancer effects. These compounds have a diminished ability to induce some of the mechanism-based side effects of NSAIDs which are indiscriminate cyclooxygenase inhibitors. In particular, the compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects. Moreover, by sparing potentially beneficial prostaglandin pathways, these agents may have enhanced efficacy over NSAIDS and/or COX-2 inhibitors.

In The American Physiological Society (1994, 267, R289-R-294), studies suggest that PGE_2-induced hyperthermia in the rat is mediated predominantly through the EP_1 receptor. WO 96/06822 (March 7, 1996), WO 96/11902 (April 25, 1996), EP 752421-A1 (January 08, 1997) and WO 01/19814 (22 March 2001) disclose compounds as being useful in the treatment of prostaglandin mediated diseases.

Accordingly the present invention provides compounds of formula (I):



(I)

wherein:

A represents an optionally substituted aryl group, or an optionally substituted 5- or 6-membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;

R^1 represents CO_2H, CN, $CONR^5R^6$, CH_2CO_2H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO_2alkyl, $SO_2NR^5R^6$, $NR^5CONR^5R^6$, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;

R^{2a} and R^{2b} independently represents hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, CN, SO_2alkyl, SR^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;

R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms may optionally be replaced by a group independently selected from NR^4, O and SO_n, wherein n is 0, 1 or 2; or R^x may be optionally substituted CQ_2-heterocyclyl, optionally substituted CQ_2-bicyclic heterocyclyl or optionally substituted CQ_2-aryl;

R^4 represents hydrogen or an optionally substituted alkyl;

R^5 represents hydrogen or an optionally substituted alkyl;

R^6 represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted SO_2heteroaryl, CN, optionally substituted CQ_2aryl, optionally substituted CQ_2heteroaryl or COR^7;

R^7 represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;

R^8 represents hydrogen, CF_3, or alkyl;

R^9 represents hydrogen, CF_3 or alkyl;
Q is independently selected from hydrogen and CH_3;
wherein when A is a 6-membered ring the R^1 substituent and pyrrole ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R^1 substituent and pyrrole ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;
or a derivative thereof.

When A is a six membered ring, preferably the R^1 substituent is attached to A in the 3 or 4-position relative to the bond attaching A to the pyrrole ring. When R^1 is CO_2H, preferably the substituent is attached to A in the 3-position relative to the bond attaching A to the pyrrole ring.

Examples of A include phenyl, naphthyl, indolyl, pyridyl, pyridazinyl, pyrazinyl or pyrimidinyl, all of which may be optionally substituted. Particular examples include optionally substituted phenyl, optionally substituted pyridyl, indolyl or naphthyl. Preferably A is pyridyl or an optionally substituted phenyl; most preferably A is optionally substituted phenyl. In an alternative embodiment A is preferably pyridyl, more preferably A is 2,6-disubstituted pyridyl. In an alternative aspect A is selected from phenyl, pyridyl, pyridazinyl, pyrazinyl and pyrimidinyl, all of which may be optionally substituted.

Examples of optional substituents for A when a phenyl group include up to four substituents, preferably up to three substituents, more preferably up to two substituents independently selected from halogen, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, NR^4R^5, NR^5COC_{1-6}alkyl, $NR^5SO_2C_{1-6}$alkyl, OR^5, C_{1-6}alkyl, SO_2C_{1-6}alkyl, $NR^5COCH_2OC_{1-6}$alkyl, optionally substituted NR^5COCH_2Oaryl, and optionally substituted NR^5COCH_2heteroaryl, wherein R^4 and R^5 are each independently selected from hydrogen and C_{1-4}alkyl; and $NR^{10}R^{11}$ wherein R^{10} and R^{11} together with the nitrogen atom to which they are attached form an optionally substituted 5- or 6-membered aliphatic heterocyclic ring wherein one of the ring carbons may be optionally replaced by another heteroatom selected from O, and SO_n wherein n is 0, 1 or 2.

Examples of substituents for the 5- or 6-membered aliphatic heterocyclic ring include oxo.

Preferably optional substituents for A when a phenyl group are selected from halogen, CF_3, $OCHF_2$, NR^4R^5, NR^5COC_{1-6}alkyl, $NR^5SO_2C_{1-6}$alkyl, OR^5, C_{1-6}alkyl, SO_2C_{1-6}alkyl, $NR^5COCH_2OC_{1-6}$alkyl, NR^5COCH_2thienyl, morpholinyl, pyrrolidinyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl and 1,1-dioxo-1λ^6-*iso*thiazolidinyl wherein R^4 and R^5 are each selected from hydrogen and C_{1-4}alkyl.

Optional substituents for A when a 5- or 6-membered heterocyclyl group include NH_2. When A is pyridyl it may be substituted on the ring nitrogen by an oxygen to give a pyridine N-oxide.

Examples of R^1 include CO_2H, CN, $CONR^4R^5$, optionally substituted $CONR^5SO_2$aryl, optionally substituted $CONR^5SO_2$heteroaryl, optionally substituted $CONR^5$aryl, optionally substituted $CONR^5$heteroaryl e.g. $CONR^5$tetrazolyl and $CONR^5$pyridyl, $CONR^5SO_2C_{1-6}$alkyl, optionally substituted $CONR^5SO_2$heteroaryl e.g. $CONR^5SO_2$-3,5-dimethylisoxazolyl, optionally substituted $CONR^5CQ_2$aryl, optionally substituted $CONR^5CQ_2$heteroaryl, optionally substituted C_{1-6}alkyl e.g. $CF_3C(OH)CF_3$, SO_2C_{1-6}alkyl, $SO_2NR^4R^5$, optionally substituted SO_2NR^5COaryl, optionally substituted SO_2NR^5COheteroaryl e.g SO_2NR^5CO-3,5-dimethylisoxazolyl, $SO_2NR^5COC_{1-6}$alkyl, optionally substituted $SO_2NR^5CQ_2$aryl, optionally substituted $SO_2NR^5CQ_2$heteroaryl; COC_{1-6}alkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycyl e.g. benzimidazolyl, or optionally substituted heterocyclyl e.g. tetrazolyl, imidazolyl, methyloxadiazolyl and oxadiazolyl; wherein R^4 and R^5 are each selected from hydrogen and C_{1-4}alkyl, and Q is selected from hydrogen and CH_3.

When R^1 is optionally substituted heterocyclyl it is preferably tetrazolyl.

Preferably R^1 represents $CONHCQ_2$aryl, $CONHCQ_2$heteroaryl, $CONHSO_2$aryl, $CONHSO_2$heteroaryl, SO_2NHCOaryl, SO_2NHCOheteroaryl all of which may be optionally substituted, CO_2H, tetrazolyl or SO_2CH_3. More preferably R^1 represents CONHCHQphenyl, $CONHSO_2$phenyl, SO_2NHCOphenyl, all of which may be optionally substituted, CO_2H, tetrazolyl or SO_2CH_3. Most preferably R^1 represents CO_2H.

Preferably aryl is optionally substituted phenyl.

Preferably Q is hydrogen.

When R^x represents an optionally substituted alkyl this group is preferably C_{1-8}alkyl, more preferably the alkyl group is CH_2C_{5-6}cycloalkyl wherein 1 or 2 of the ring carbon atoms may optionally be replaced by a group independently selected from NR^4, O or SO_n, wherein n is 0, 1 or 2 and R^4 is selected from hydrogen and C_{1-4}alkyl.

Examples of R^x include $CH_2CH(CH_3)_2$, CH_2cyclohexyl, CH_2tetrahydrofuranyl, CH_2 tetrahydropyranyl, optionally substituted CH_2-heterocyclyl e.g. CH_2methylisoxazolyl, optionally substituted CH_2-bicyclic heterocyclyl e.g. CH_2benzofurazanyl, optionally substituted CH_2naphthyl or optionally substituted CH_2-phenyl. Examples of substituents for CH_2phenyl and CH_2naphthyl include up to 4 substituents independently selected from halogen, optionally substituted C_{1-6}alkyl, C_{1-4}haloalkyl, C_{1-6}haloalkoxy, optionally substituted phenyl, and optionally substituted OC_{1-6}alkyl. Particular examples include up to to three substituents independently selected from halogen, C_{1-4}alkyl, CF_3, phenyl, OC_{1-4}alkyl and $OCHF_2$. Preferred substituents include up to three substituents independently selected from chloro, bromo and fluoro.

In a preferred aspect R^x is optionally substituted CH_2-phenyl.

Preferably R^{2a} is hydrogen.

Preferably R^{2b} represents hydrogen, fluoro, chloro, bromo, optionally substituted C_{1-4}alkyl, e.g. CF_3, and CH_3, phenyl or SO_2C_{1-4}alkyl, e.g. SO_2CH_3. More preferably R^{2b} represents hydrogen, fluoro, chloro, bromo, or CF_3.

Preferably R^{2b} is positioned on the phenyl ring *meta* to the pyrrole group and *para* to the oxy substituent.

R^4 is preferably hydrogen or C_{1-6}alkyl, more preferably hydrogen or C_{1-4}alkyl.

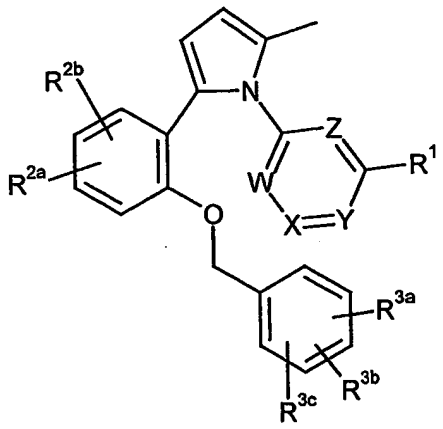
R^5 is preferably hydrogen or C_{1-6}alkyl, more preferably hydrogen or C_{1-4}alkyl.

R^8 preferably represents CH_3.

R^9 preferably represents hydrogen.

In an alternative aspect:
A represents an optionally substituted phenyl, or a 5- or 6- membered heterocyclyl group;
R^1 represents CO_2R^4, $CONR^5R^6$, $CH_2CO_2R^4$, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkenyl, SO_2C_{1-6}alkyl, $SO_2NR^5R^6$, $NR^5CONR^5R^6$, tetrazolyl or $CONR^5R^6$;
R^{2a} and R^{2b} independently represent hydrogen, halo, CF_3 optionally substituted C_{1-6}alkyl, CN, SO_2R^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;
R^x represents optionally substituted C_{1-8}alkyl or optionally substituted CH_2phenyl;
R^4 represents hydrogen or an optionally substituted C_{1-6}alkyl;
R^5 represents hydrogen or an optionally substituted C_{1-6}alkyl;
R^6 represents hydrogen or an optionally substituted C_{1-6}alkyl, optionally substituted - SO_2aryl, optionally substituted SO_2heterocyclyl group, CN or COR^7;
R^7 represents hydrogen or an optionally substituted aryl;
R^8 represents hydrogen, CF_3 or C_{1-6}alkyl;
R^9 represents hydrogen, Cl, Br, I, CF_3 or C_{1-6}alkyl;
wherein R^1 is attached to the group A in the 3 position relative to the bond attaching A to the pyrrole ring;
or a pharmaceutically acceptable derivative thereof.

Preferred compounds of formula (I) are compounds of formula (Ia):



(Ia)

wherein:

R^1 is CO_2H;

R^{2a} and R^{2b} are independently selected from hydrogen, halo, phenyl, optionally substituted C_{1-6}alkyl e.g. C_{1-4}alkyl and CF_3, CN, SC_{1-6}alkyl, or SO_2C_{1-6}alkyl;

R^{3a}, R^{3b}, and R^{3c} are independently selected from hydrogen, halo, optionally substituted OC_{1-6}alkyl, e.g $OCHF_2$, phenyl or optionally substituted C_{1-6}alkyl e.g. CF_3;

W, X, Y and Z each represents CR^{12} or N wherein at least two of W, X, Y or Z is CR^{12}; and when each of W, X, Y, and Z is CR^{12} then each R^{12} is independently selected from hydrogen, halogen, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, NR^4R^5, NR^5COC_{1-6}alkyl, $NR^5SO_2C_{1-6}$alkyl, OR^5, C_{1-6}alkyl, SO_2C_{1-6}alkyl, $NR^5COCH_2OC_{1-6}$alkyl, NR^5COCH_2aryl, NR^5COCH_2heteroaryl wherein R^4 and R^5 are each independently selected from hydrogen and C_{1-4}alkyl; and $NR^{10}R^{11}$ wherein R^{10} and R^{11} together with the nitrogen atom to which they are attached form an optionally substituted 5- or 6-membered aliphatic heterocyclic ring wherein one of the ring carbons may be optionally replaced by another heteroatom selected from O and SO_n wherein n is 0, 1 or 2., and when at least one of W, X, Y and Z represents N then each R^{12} is selected from hydrogen and NH_2;

or derivatives thereof.

In an alternative aspect of compounds of formula (Ia):

R^1 is CO_2R^4;

R^{2a} and R^{2a} are independently selected from hydrogen, halo, optionally substituted C_{1-6}alkyl, CN or SO_2C_{1-6}alkyl;

R^{3a} and R^{3b} are independently selected from hydrogen, halo or an optionally substituted OC_{1-6}alkyl, or C_{1-6}alkyl;

R^{3c} is hydrogen;

R^4 is hydrogen or an optionally substituted C_{1-6}alkyl;

W, X, Y and Z represents CH or N wherein at least one of W, X, Y or Z is CH;

or pharmaceutically acceptable derivatives thereof.

Preferably R^{2a} and R^{2b} are independently selected from hydrogen, chloro, fluoro, bromo and CF_3 More preferably R^{2a} is hydrogen and R^{2b} is selected from hydrogen, chloro, fluoro, bromo and CF_3.

Preferably R^{3a}, R^{3b} and R^{3c} are independently selected from hydrogen, CF_3, chloro, fluoro and bromo.

Preferably one of W, X, Y and Z is selected from N and CR^{12} and the remaining atoms are CR^{12}. More preferably Z is N and W, X and Y are CR^{12}. Most preferably Z is N and W, X and Y are CH. Alternatively W, X, Y and Z are each selected from CR^{12}

Examples of compounds of formula (I) include:
3-{2-[2-(Benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[2-(Benzyloxy)-5-chloro-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5 –Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-Phenyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-Chloro-2-(cyclohexylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-1-pyrrol-1-yl}-methanesulfonyl benzene;
3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-1-pyrrol-1-yl}-methanesulfonyl benzene;
3-{2-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-Bromo-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-Bromo-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-Bromo-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[2-(4-Methoxy-benzyloxy)-phenyl]-pyrrol-1-yl}-benzoic acid;
3-{2-[2-(3,4-Dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[2-(2-Chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[2-(4-Chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-Chloro-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid;
5-{2-[2-(4-Methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid;
5-{2-[2-(4-Chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid;
5-{2-[2-(3,4-Dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid;
5-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid;
5-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid;

5-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid;
5-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid;
and derivatives thereof.

Preferred compounds include the compounds of Examples 11, 33, 41, 46, 49, 55, 60, 72, 76, 85, 88, 103, 106, 112, 122, 125, 150, 155, 157, 175, 176, 180, 183, 188, 191, 200, 207, 209, 211, 222, 225, 234, 235, 236, 237, 239, 240, 241, 245, 250, 254, 261, 262, 278, 283, 295, 306, 314, 316, 332, 338, 348, 353, 358, 356, 367, 376, 383, 385, 387, 388 and 392; and derivatives thereof.

More preferred compounds are the compounds of Examples 46, 60, 183, 222, 225, 234, 235, 236, 237, 239, 240, 241, 250, 254, 283 and 348; and derivatives thereof.

Preferably compounds are selective for EP_1 over EP_2, EP_3 and EP_4. More preferably the compounds are 100 fold selective, more preferably 1000 fold selective for EP_1.

The invention is described using the following definitions unless otherwise indicated.

Suitable derivatives are pharmaceutically acceptable derivatives.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of such ester or solvate of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds, and that the compounds of formula (I) may be derivatised at more than one position.

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse , *J. Pharm. Sci.*, 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine,

N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropyl amine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acid.

Preferred examples of pharmaceutically acceptable salts include those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids.

The salts and/or solvates of the compounds of the formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the preparation of pharmaceutically acceptable salts and/or solvates of compounds of formula (I) or the compounds of the formula (I) themselves, and as such form another aspect of the present invention.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and if crystalline, may be optionally hydrated or solvated. This invention includes in its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Suitable solvates include pharmaceutically acceptable solvates, such as hydrates.

Solvates include stoichiometric solvates and non-stoichiometric solvates.

The terms "halogen" or "halo" are used to represent fluorine, chlorine, bromine or iodine, more preferably fluorine, chlorine and bromine.

The term "alkyl" means a straight, branched or cyclic chain alkyl group or combinations thereof, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopentyl or cyclohexyl or combinations thereof such as cyclohexylmethyl and cyclopentylmethyl. Unless otherwise defined, preferably "alkyl" is C_{1-8}alkyl, more preferably "alkyl" is C_{1-6}alkyl.

The term "alkoxy" means a straight, branched or cyclic chain alkyl group having an oxygen atom attached to the chain, for example a methoxy, ethoxy, n-propoxy, i-propoxy, n-

butoxy, s-butoxy, t-butoxy group, pentoxy, hexyloxy group, cyclopentoxy or cyclohexyloxy group. Preferably "alkoxy" is C_{1-6} alkoxy.

The term "haloalkyl" means an alkyl group, including straight, branched or cyclic structures, of the indicated number of carbon atoms in which one or more hydrogen atoms have been replaced by halogen atoms, with up to complete substitution of all hydrogen atoms with halo groups. Preferably "haloalkyl" is C_{1-6}haloalkyl, more preferably C_{1-4}haloalkyl. C_{1-6}haloalkyl, for example, includes C_{1-6}fluoroalkyl, e.g. CF_3, CF_2CF_3, CHF_2, CH_2F and the like.

The term "haloalkoxy" means an alkoxy group, including straight, branched or cyclic structures, of the indicated number of carbon atoms in which one or more hydrogen atoms have been replaced by halogen atoms, with up to complete substitution of all hydrogen atoms with halo groups. . Preferably "haloalkoxy" is C_{1-6}haloalkoxy, more preferably C_{1-4}haloalkoxy. C_{1-6}haloalkoxy, for example, includes C_{1-6}fluoroalkoxy e.g. OCF_3, $OCHF_2$, OCF_2CF_3 and the like.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon to carbon double bond. Preferably "alkenyl" is C_{2-6}alkenyl. C_{2-6}alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

The term "aliphatic heterocyclyl" as a group or as part of a group means an aliphatic five or six membered ring which contains from 1 to 4 heteroatoms selected from nitrogen, oxygen or sulfur and unsubstituted or substituted by, for example, up to three substituents selected from halo, NH_2, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy and oxo. Examples of 5-membered aliphatic heterocyclyl groups include pyrrolidinyl, dioxolanyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, pyrazolidinyl, and tetrahydrofuranyl. Examples of 6-membered aliphatic heterocyclyl groups include morpholinyl, thiomorpholinyl, piperidinyl, dithianyl, piperazinyl and tetrahydropyranyl.

The term "heterocyclyl" as a group or as part of a group means an aromatic or non-aromatic five or six membered ring which contains from 1 to 4 heteroatoms selected from nitrogen, oxygen or sulfur and unsubstituted or substituted by, for example, up to three substituents selected from halo, oxo, NH_2, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}haloalkoxy. Examples of 5- membered heterocyclyl groups include furyl, dioxalanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazinyl, isothiazolyl, isoxazolyl, thiophenyl, pyrazolyl or tetrazolyl. Examples of 6-membered heterocyclyl groups are pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl or tetrazinyl.

The term "aryl" as a group or part of a group means a 5- or 6- membered aromatic ring, for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the

rings is aromatic, for example naphthyl. An aryl group may be optionally substituted by one or more substituents, for example up to 4, 3 or 2 substituents. Preferably the aryl group is naphthyl or phenyl, more preferably phenyl.

The term "heteroaryl" as a group or as part of a group means a monocyclic five or six membered aromatic ring, or a fused bicyclic aromatic ring system comprising two of such monocyclic five or six membered aromatic rings. These heteroaryl rings contain one or more heteroatoms selected from nitrogen, oxygen or sulfur, where N-oxides, sulfur oxides and sulfur dioxides are permissible heteroatom substitutions. A heteroaryl group may be optionally substituted by one or more substituents, for example up to 3 or up to 2 substituents, selected from, for example, halo, NH_2, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}haloalkoxy. Examples of "heteroaryl" used herein include furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuryl, benzothienyl, indolyl, and indazolyl.

The term "bicyclic heterocyclyl" when used herein means a fused bicyclic aromatic or non-aromatic bicyclic heterocyclyl ring system comprising up to four, preferably one or two, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring. . A bicyclic heterocyclic group may be optionally substituted by one or more substituents, for example up to 3 or up to 2 substituents, selected from, for example, oxo, halo, NH_2, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, and C_{1-4}haloalkoxy. Examples of bicyclic heterocyclyl groups include quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, benzothiazolyl, benzoxadiazolyl, benzthiadiazolyl, indolyl, benztriazolyl or naphthyridinyl.

When the heteroatom nitrogen replaces a carbon atom in an alkyl group, or when nitrogen is present in a heteroaryl, heterocyclyl or bicyclic heterocyclyl group, the nitrogen atom will, where appropriate be substituted by one or two substituents selected from hydrogen and C_{1-6}alkyl, preferably hydrogen and C_{1-6}alkyl, more preferably hydrogen.

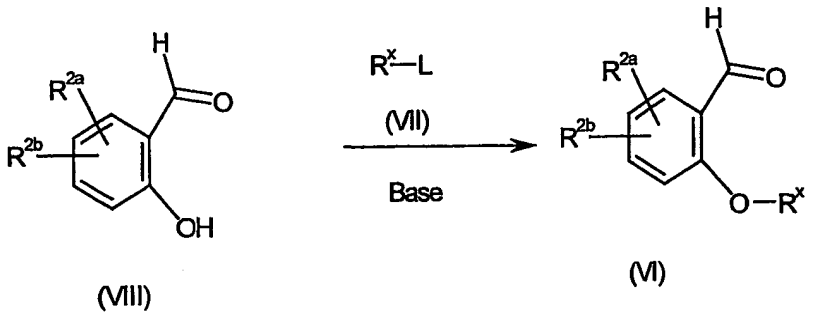
Optional substituents for alkyl or alkenyl groups include OH, CO_2R^4, NR^4R^5, (O), OC_{1-6}alkyl or halo, wherein R^4 and R^5 are selected from hydrogen and C_{1-6}alkyl . An alkyl or alkenyl group may be substituted by one or more optional substituents, for example up to 5, 4, 3, or 2 optional substituents.

Optional substituents for alkoxy groups include OH, CO_2R^4, NR^4R^5, (O), OC_{1-6}alkyl or halo, wherein R^4 and R^5 are selected from hydrogen and C_{1-6}alkyl . An alkoxy group may be substituted by one or more optional substituents, for example up to 5, 4, 3, or 2 optional substituents.

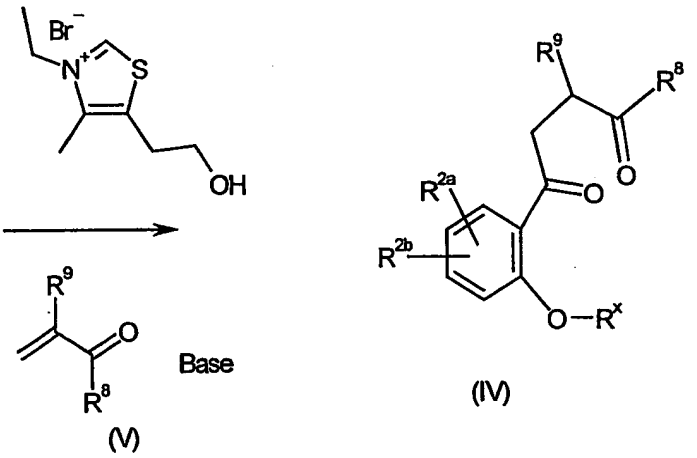
Unless otherwise defined, examples of optional substituents for aryl, heteroaryl or heterocyclyl moieties as a group or part of a group are selected from optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkoxy and C_{1-6}haloalkyl, C_{1-6}haloalkoxy and halogen.

Compounds of formula (I) can be prepared as set forth in the following Schemes and in the Examples and references cited therein The following processes form another aspect of the present invention.

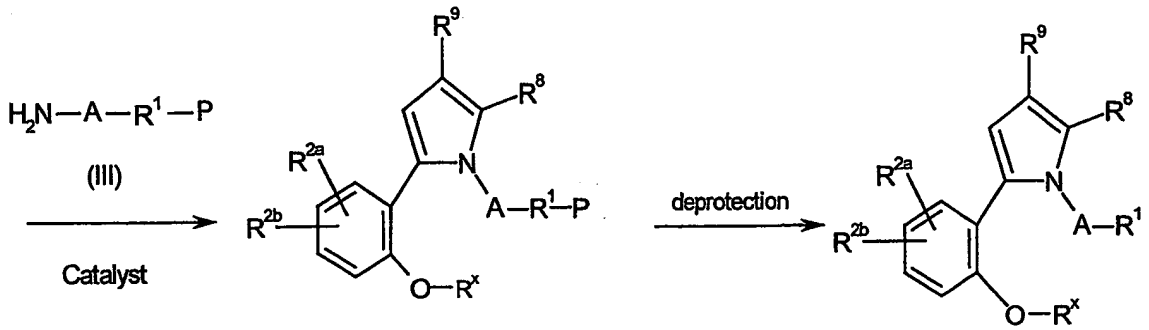
For example, compounds of formula (I) may be prepared by the general route below:



(VIII) (VI)



(V) (IV)



(II) (I)

wherein L is a leaving group for example halo, e.g. bromo; P is an optional protecting group, for example methyl or ethyl esters; A, R^8,R^9, R^{2a}, R^{2b}, R^1 and R^x are as hereinbefore defined for compounds of formula (I).

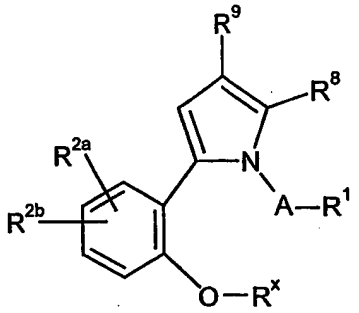
When R^1 is CO_2H, a suitable protecting group P is an ester forming group such as C_{1-4}alkyl or optionally substituted benzyl. Suitable reaction conditions for the deprotection of a compound of formula (II) include hydrolysis effected by e.g. heating in ethanolic sodium hydroxide solution, or hydrogenation.

Suitable reaction conditions for the reaction of a compound of formula (IV) with a compound of formula (III) to give a pyrrole of formula (II) include heating with an acid catalyst e.g. p-toluenesulfonic acid in a solvent such as toluene. Reviews of pyrrole synthesis can be found in e.g. A. Triebs, *Chem. Ber.*, 1957, 90, 79-84, E. Baltazzi *et al*, *Chem. Rev.*, 1963, 63, 511, and R.A. Jones, *Advances in Heterocyclyl Chemistry*, 1970, 11, 383.

Suitable reaction conditions for the conversion of a compound of formula (VI) to a compound of formula (IV) include heating the compound of formula (VI) with a vinyl ketone of formula (V) in the presence of 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide and an organic base, for example triethylamine, in a solvent, for example ethanol.

Suitable reaction conditions for the preparation of a compound of formula (VI) include reacting a salicylaldehyde of formula (VIII) with a compound R^x-L of formula (VII) in N,N-dimethylformamide solution the presence of base, e.g. potassium carbonate.

Accordingly the present invention also provides a process for the preparation of a compound of formula (I) or a derivative thereof:



(I)

wherein:

A represents an optionally substituted aryl group, or an optionally substituted 5- or 6-membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;

R^1 represents CO_2H, CN, $CONR^5R^6$, CH_2CO_2H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO_2alkyl, $SO_2NR^5R^6$, $NR^5CONR^5R^6$, COalkyl,

2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;

R^{2a} and R^{2b} independently represents hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, CN, SO_2alkyl, SR^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;

R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms may optionally be replaced by a group independently selected from NR^4, O and SO_n, wherein n is 0, 1 or 2: or R^x may be optionally substituted CQ_2-heterocyclyl, optionally substituted CQ_2-bicyclic heterocyclyl or optionally substituted CQ_2-aryl;

R^4 represents hydrogen or an optionally substituted alkyl;

R^5 represents hydrogen or an optionally substituted alkyl;

R^6 represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted SO_2heteroaryl, CN, optionally substituted CQ_2aryl, optionally substituted CQ_2heteroaryl or COR^7;

R^7 represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;

R^8 represents hydrogen, CF_3, or alkyl;

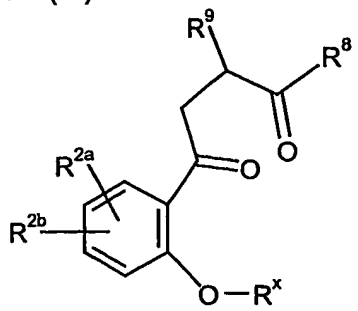
R^9 represents hydrogen, CF_3 or alkyl;

Q is independently selected from hydrogen and CH_3;

wherein when A is a 6-membered ring the R^1 substituent and pyrrole ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R^1 substituent and pyrrole ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;

comprising:

reacting a compound of formula (IV):



(IV)

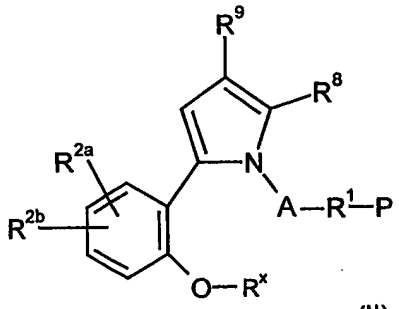
wherein R^8, R^9, R^{2a}, R^{2b}, and R^x are as hereinbefore defined above for a compound of formula (I);

with a compound of formula (III):

$$H_2N—A—R^1—P$$

(III)

wherein A and R^1 are as hereinbefore defined above for a compound of formula (I), and P is an optional protecting group;
to give a compound of formula (II):

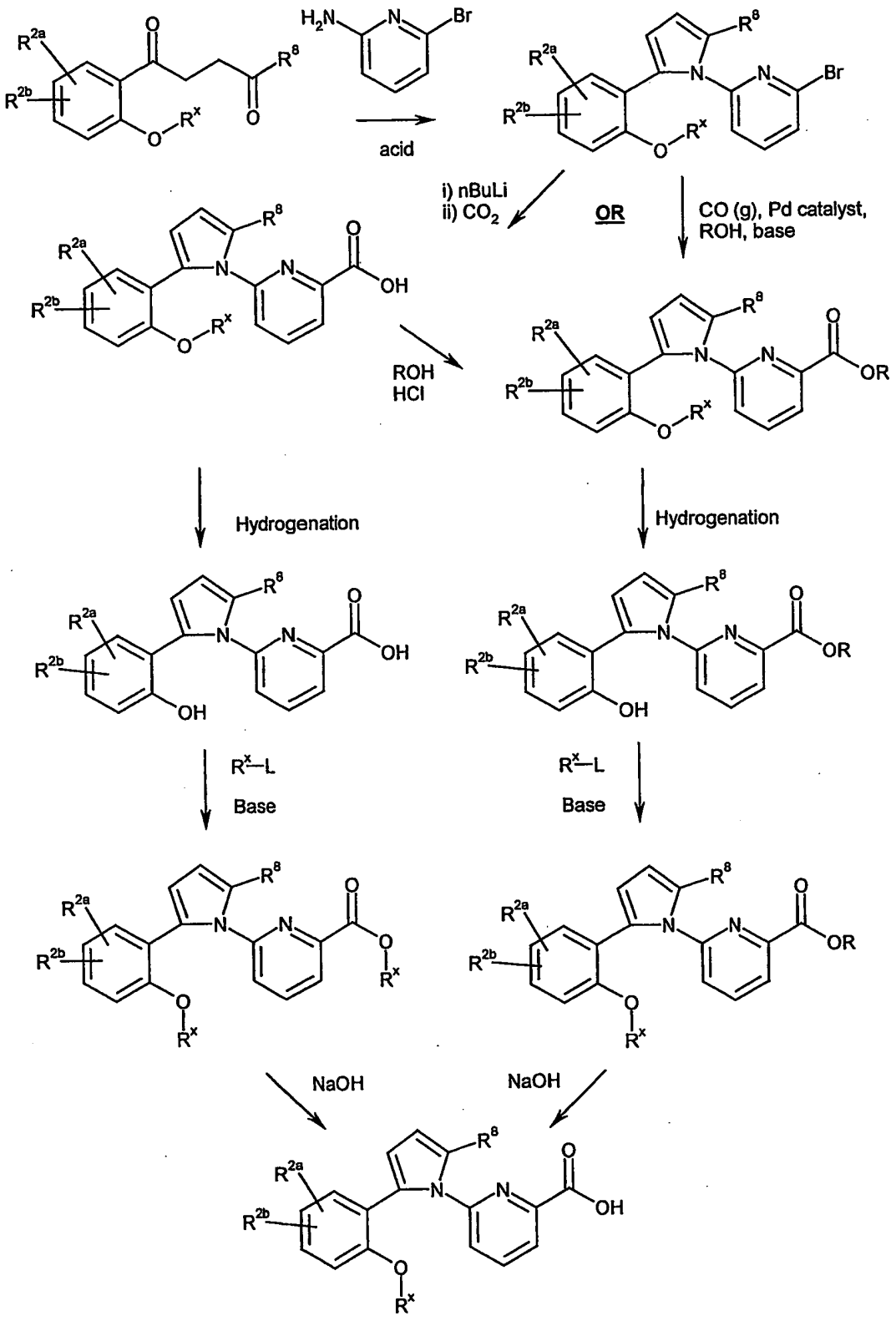


(II)

wherein P, A, R^8, R^9, R^{2a}, R^{2b}, R^1 and R^x are as hereinbefore defined;
and where required converting:
one group A to another group A, and/or
one group R^{2a} to another group R^{2a}; and/or
one group R^{2b} to another group R^{2b};and/or
one group R^x to another group R^x;
and where required carrying out the following optional steps in any order:
a) effecting deprotection; and/or
b) converting one group R^1 to another group R^1; and/or
c) forming a derivative of the compound of formula (I) so formed.

A group R^1 may be converted to another group R^1 by use of conventional organic transformations known to those skilled in the art. For example $R^1 = CO_2H$ may be converted to an amide, e.g. $CONHCQ_2$aryl or $CONHCQ_2$heteroaryl wherein Q is hydrogen or CH_3, by conventional methods for the preparation of amides as described in, for example, Richard Larock, *Comprehensive Organic Transformations,* 2nd edition, Wiley-VCH, ISBN 0-471-19031-4.

Compounds of formula (I) wherein A is a 2,6-disubstituted pyridine may also be prepared by the route described below:



wherein L is a leaving group e.g. bromo, R is C_{1-4}alkyl, R^{2a} and R^{2b} are selected from hydrogen, halo and CF_3, and R^8, and R^x are as defined above for compounds of formula (I).

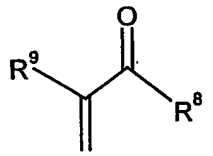
Compounds of formula (III), (V), (VII) and (VIII) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide are commercially available, or readily prepared by methods known to those skilled in the art.

Compounds of formula (III):

$$H_2N—A—R^1—P$$

wherein P is as defined above and R^1 and A are as hereinbefore defined for compounds of formula (I) are commercially available or may readily be prepared from commercially available materials according to known methods for preparing amines, e.g. using methods as described in the Examples. Methods for the preparation of amines are reviewed in *The Amino Group*, S. Patai (Ed), Interscience, New York 1968, and references cited therein. The preparation of amines is also described in Richard Larock, *Comprehensive Organic Transformations*, 2nd edition, pages 753 to 879, Wiley-VCH, ISBN 0-471-19031-4.

Intermediates of formula (V):



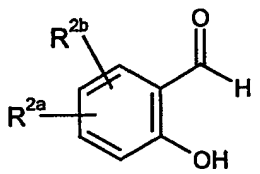
wherein $R^8$and R^9 are as hereinbefore defined for compounds of formula (I) are commercially available or may be readily prepared according to known methods for the preparation of vinyl ketones. For example, $F_3CCOCHCH_2=CH_2$ may be prepared according to the method of M. Tordeux *et al*, *J. Fluorine Chemistry*, 1982, 20(3), 301-306.

Intermediates of formula (VII):

$$R^x—L$$

wherein L is as defined above and R^x is as defined for compounds of formula (I) are commercially available, or may be readily prepared by known transformations of commercially available compounds.

Intermediates of formula (VIII):



wherein R^{2a} and R^{2b} are as defined for compounds of formula (I) are commercially available, or may readily be prepared by methods known to those skilled in the art, for example from suitable commercially available starting materials using methods as described in the examples. The preparation of aldehydes is reviewed in *The Chemistry of the Carbonyl Group*, S. Patai (Ed), Interscience, New York, 1966, and references cited therein.

Certain substituents in any of the reaction intermediates and compounds of formula (I) may be converted to other substituents by conventional methods known to those skilled in the art. Examples of substituents which may be converted include one group R^{2a} to another group R^{2a}, one group R^{2b} to another group R^{2b}; one group R^x to another group R^x; and substituent on a group A to another substituent on a group A. Examples of such transformations include the reduction of a nitro group to give an amino group; alkylation and amidation of amino groups; hydrolysis of esters, alkylation of hydroxy and amino groups; and amidation and esterification of carboxylic acids. Such transformations are well known to those skilled in the art and are described in for example, Richard Larock, *Comprehensive Organic Transformations,* 2nd edition, Wiley-VCH, ISBN 0-471-19031-4.

For example, when R^x is p-methoxybenzyl, cleavage of the ether to give the phenol is carried out using, for example, using acid e.g. HCl/dioxane or using sodium methanethiolate. Conversion to another R^x group, for example a substituted benzyl group, may be effected by reaction of the phenol with a suitable substituted benzyl bromide. The skilled person will appreciate that conversion of the protecting group P to another protecting group P may also occur under the reaction conditions used. When R^x is benzyl, cleavage of the ether to give the phenol may be carried out by hydrogenation according to known methods e.g. H_2-Pd/C or NH_4CO_2H-Pd/C. The resulting phenol can then be converted to another group R^x as described above.

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. The skilled person will recognise when a protecting group is required. Standard protection and deprotection techniques, such as those described in Greene T.W. 'Protective groups in organic synthesis', New York, Wiley (1981), can be used. For example, carboxylic acid groups can be protected as esters. Deprotection of such groups is achieved using conventional procedures known in the art. It will be appreciated that protecting groups may be interconverted by conventional means.

It is to be understood that the present invention encompasses all isomers of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoismers, including mixtures thereof. The different isomeric forms may be

separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The compounds of the invention bind to the EP_1 receptor and are therefore useful in treating EP_1 receptor mediated diseases.

In view of their ability to bind to the EP_1 receptor, the compounds of the invention may be useful in the treatment of the disorders that follow. Thus, the compounds of formula (I) may be useful as analgesics. For example they may be useful in the treatment of chronic articular pain (e.g. rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea. The compounds of the invention may also be useful in the treatment of visceral pain.

The compounds of the invention may be particularly useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of formula (I) may also be useful in the treatment of fever.

The compounds of formula (I) may also be useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myaesthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of formula (I) are also useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) are also effective in increasing the latency of HIV infection.

The compounds of formula (I) are also useful in the treatment of diseases of abnormal platelet function (e.g. occlusive vascular diseases).
The compounds of formula (I) are also useful for the preparation of a drug with diuretic action.

The compounds of formula (I) are also useful in the treatment of impotence or erectile dysfunction.

The compounds of formula (I) are also useful in the treatment of bone disease characterised by abnormal bone metabolism or resorbtion such as osteoporosis (especially postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cacchexia, calculosis, lithiasis (especially urolithiasis), solid carcinoma, gout and ankylosing spondylitis, tendinitis and bursitis.

The compounds of formula (I) are also useful for attenuating the hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors.

The compounds of formula (I) are also useful in the treatment of cardiovascular diseases such as hypertension or myocardiac ischemia; functional or organic venous insufficiency;

varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g. septic shock).

The compounds of formula (I) are also useful in the treatment of neurodegenerative diseases and neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, ALS, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment. The compounds of formula (I) are also useful in the treatment of neuroprotection and in the treatment of neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

The compounds of formula (I) are also useful in the treatment of tinnitus.

The compounds of formula (I) are also useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine. The compounds of formula (I) are also useful in the treatment of complications of Type 1 diabetes (e.g. diabetic microangiopathy, diabetic retinopathy, diabetic nephropathy, macular degeneration, glaucoma), nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

The compounds of formula (I) are also useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cirrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE_2 at EP_1

receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a yet further aspect of the invention we provide a method of treating a human or animal subject suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder.

According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as inflammatory pain, neuropathic pain or visceral pain.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in

a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative. Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.
The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The EP_1 receptor compounds for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib or COX-189; 5-lipoxygenase inhibitors; NSAID's, such as diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor antagonists; gabapentin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; $5HT_1$ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; nicotinic acetyl choline (nACh) receptor modulators; glutamate receptor modulators, for example modulators of the NR2B ssubtype; EP_4 receptor ligands; EP_2 receptor ligands; EP_3 receptor ligands; EP_4 antagonists; EP_2 antagonists and EP_3 antagonists; cannabanoid receptor ligands; bradykinin receptor ligands and vanilloid receptor ligand. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

Additional COX-2 inhibitors are disclosed in US Patent Nos. 5,474,995 US5,633,272; US5,466,823, US6,310,099 and US6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO99/12930, WO00/26216, WO00/52008, WO00/38311, WO01/58881 and WO02/18374.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A proposed daily dosage of compounds of formula (I) or their pharmaceutically acceptable derivatives for the treatment of man is from 0.01 to 30 mg/kg body weight per day and more particularly 0.1 to 10 mg/kg body weight per day, calculated as the free base, which may be administered as a single or divided dose, for example one to four times per day The dose range for adult human beings is generally from 8 to 2000 mg/day, such as from 20 to 1000 mg/day, preferably 35 to 200 mg/day, calculated as the free base.

The precise amount of the compounds of formula (I) administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors including the age and sex of the patient, the precise condition being treated and its severity, and the route of administration.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

EXAMPLES

Abbreviations

Definitions of abbreviations used herein: ethyl acetate (EtOAc), N,N-dimethylformamide (DMF), hexand (hex), dimethylsulfoxide (DMSO), dichloromethane (DCM), tetrahydrofuran (THF), 1-methyl-2-pyrrolidinone (NMP), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC or EDAC), triethylamine (TEA), p-toluenesulfonic acid (pTSA), 1-hydroxybenzotriazole (HOBt), p-methoxybenzyl (PMB), 4-dimethylaminopyridine (DMAP), Mass Directed Auto-Purification System (MDAP).

Example 1: 3-{2-[2-(Benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 1-(2-Benzyloxy-phenyl)-pentane-1,4-dione

A mixture of 2-benxyloxy-benzaldehyde (3ml, 18.93mmol), methyl vinyl ketone (1.6ml, 19.24mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (720mg, 2.86mmol, 0.15eq) and triethylamine (4ml, 28.75mmol) was heated in ethanol (6.3ml, 3M) at reflux for 24 hours. Upon cooling, the mixture was diluted with EtOAc and washed with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4) filtered and concentrated. The residue was purified by chromatography with hexane containing a gradient of EtOAc (5-20%) to give the title compound as an oil (3.369g, 63%).

^1H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 2.77 (2H, t, J=6Hz), 3.27 (2H, t, J=6Hz), 4.11 (2H, q, J=7Hz), 5.16 (2H, s), 6.97-7.05 (2H, m), 7.20-7.50 (6H, m's excess), 7.74 (1H, dd, J=2Hz, J=8Hz).

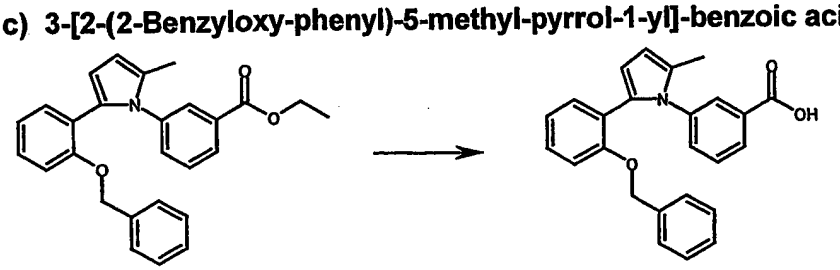
b) 3-[2-(2-Benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-benzoic acid ethyl ester

1-(2-Benzyloxy-phenyl)-pentane-1,4-dione (575mg, 2.04mmol), ethyl-3-aminobenzoate (0.37ml, 2.48mmol) and pTSA (20mg) were heated in toluene (20ml, 0.1M) at reflux for 23 hours. Upon cooling, the mixture was diluted with EtOAc and washed with 2 MHCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, with hexane containing a gradient of EtOAc (5-10%) as eluant, to give the desired compound (739mg, 88%).

^1H NMR (400MHz, $CDCl_3$) 1.30 (3H, t, J=7Hz), 2.16 (3H, s), 4.27 (2H, q, J=7Hz), 4.78 (2H, s), 6.14 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.65 (1H, d, J=9Hz), 6.85 (1H, t, J=8Hz), 7.05-7.15 (4H, m), 7.18-7.32 (5H, m' excess), 7.76 (1H, s), 7.89 (1H, d, J=8Hz).

LC/MS t=3.85 min [MH+] 412

c) 3-[2-(2-Benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-benzoic acid



3-[2-(2-Benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-benzoic acid ethyl ester (203mg, 0.49mmol) was heated with DMF (3ml) and 2M NaOH (2ml) in a reacti-vial at 85°C for 24

hrs. The mixture was cooled to room temperature and diluted with EtOAc, washed with 2M HCl then dried (Na_2SO_4), filtered and evaporated to give the title compound (42.7mg, 23%).

^{1}H NMR (400MHz, *d*6-DMSO) 2.07 (3H, s), 4.84 (2H, s), 6.05 (1H, d, J=3Hz), 6.18 (1H, d, J=3Hz), 6.78-6.87 (2H, m), 7.05-7.20 (4H, m), 7.22-7.36 (4H, m), 7.42 (1H, t, J=8Hz), 7.55 (1H, s), 7.84 (1H, d, J=8Hz), 13.05 (1H, s).

LC/MS t=3.54 min [MH+] 384, [MH-] 382.

Example 2: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 2-Benzyloxy-5-chloro-benzaldehyde

5-Chlorosalicylaldehyde (10.094g, 64.64mmol), benzyl bromide (11.5ml, 96.70mmol) and K_2CO_3 (17.935g, 13.00mmol) were heated in DMF (65ml) at 60°C for 18hrs. Upon cooling to room temperature, Et_2O and H_2O were added. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the title compound (15.850g, 100%).

^{1}H NMR (400MHz, $CDCl_3$) 5.18 (2H, s), 7.00 (1H, d, J=9Hz), 7.32-7.44 (5H, m's excess), 7.47 (1H, dd, J=3Hz, J=9Hz), 7.80 (1H, d, J=3Hz), 10.50 (1H, s).

b) 1-[5-Chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione

A mixture of 2-benzyloxy-5-chloro-benzaldehyde (4.044g, 16.41mmol), methyl vinyl ketone (1.64ml, 19.73mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (654mg, 2.60mmol, 0.15eq) and triethylamine (3.42ml, 28.75mmol) was heated in ethanol (5.5ml, 3M) at reflux for 5 hours. Upon cooling, the mixture was diluted with EtOAc and washed with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4) filtered and concentrated. The residue was purified by chromatography with *iso*-hexane containing a gradient of EtOAc (5-15%) to give the title compound as an oil (4.011g, 81%).

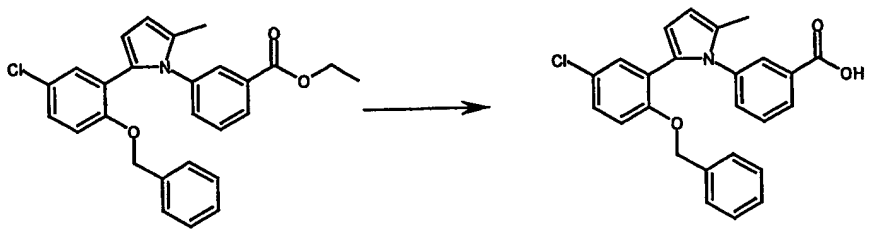
^{1}H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 2.78 (2H, d, J=6Hz), 3.23 (2H, d, J=6Hz), 5.15 (2H, s), 6.95 (1H, d, J=9Hz), 7.23-7.50 (6H, m's excess), 7.70 (1H, d, J=3Hz).

c) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

1-[5-Chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione (1.015g, 3.38mmol), ethyl-3-aminobenzoate (0.60ml, 4.02mmol) and pTSA (50mg) were heated in toluene (34ml, 0.1M) at reflux for 2.5 hours. Upon cooling, the mixture was diluted with EtOAc and washed with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography with hexane containing a gradient of EtOAc (5-10%) as eluant, to give the desired compound (906mg, 60%).

^{1}H NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7Hz), 2.15 (3H, s), 4.28 (2H, q, J=7Hz), 4.72 (2H, s), 6.13 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.54 (1H, d, J=9Hz), 7.00-7.08 (3H, m), 7.12 (1H, d, J=8Hz), 7.23 (1H, d, J=3Hz), 7.27-7.34 (4H, m's excess), 7.74 (1H, s), 7.91 (1H, d, J=8Hz).

d) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (144.7mg, 0.32mmol) was heated in a mixture of EtOH (3ml) and 2M NaOH (1ml) at reflux for 15 hours. Upon cooling, the mixture was diluted with EtOAc, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (135.1mg, 100%).
^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.72 (2H, s), 6.14 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.56 (1H, d, J=9Hz), 7.00-7.19 (3H, m), 7.17 (1H, d, J=8Hz), 7.21-7.35 (5H, m's excess), 7.78 (1H, s), 7.96 (1H, d, J=8Hz).

Example 3: 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 2-Benzyloxy-5-bromo-benzaldehyde

5-Bromosalicylaldehyde (10.045g, 49.98mmol), benzyl bromide (8.9ml, 75.00mmol) and K_2CO_3 (13.800g, 99.99mmol) were heated in DMF (50ml, 1M) at 60°C for 4hrs. Upon cooling to room temperature, Et_2O and H_2O were added. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the title compound (14.500g, 100%).
^{1}H NMR (400MHz, $CDCl_3$) 5.18 (2H, s), 6.95 (1H, d, J=9Hz), 7.27-7.50 (5H, m's, excess), 7.60 (1H, dd, J=3Hz, J=9Hz), 7.94 (1H, d, J=3Hz), 10.48 (1H, s).

b) 1-[5-Bromo-2-(benzyloxy)-phenyl]-pentane-1,4-dione

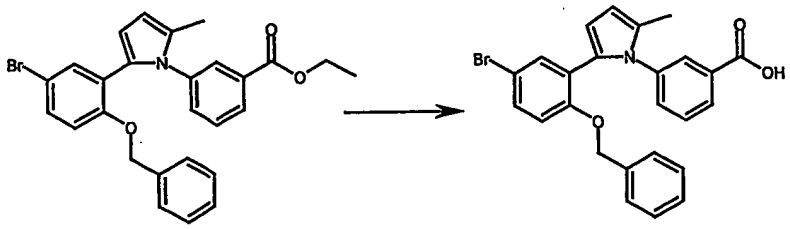
A mixture of 2-benzyloxy-5-bromo-benzaldehyde (4.079g, 14.02mmol), methyl vinyl ketone (1.40ml, 16.84mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (589mg, 2.34mmol, 0.15eq) and triethylamine (2.93ml, 21.06mmol) was heated in ethanol (4.7ml, 3M) at reflux for 5 hours. Upon cooling, the mixture was diluted with EtOAc and washed with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4) filtered and concentrated. The residue was purified by chromatography with *iso*-hexane containg a gradient of EtOAc (5-10%) to give the title compound as an oil (3.780g, 78%).
^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 2.77 (2H, t, J=6Hz), 3.22 (2H, d, J=6Hz), 5.15 (2H, s), 6.90 (1H, d, J=9Hz), 7.22-7.48 (5H, m's excess), 7.51 (1H, d, J=1.5Hz, J=9Hz), 7.84 (1H, d, J=1.5Hz).

c) 3-[2-(5-Bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-benzoic acid ethyl ester

1-[5-Bromo-2-(benzyloxy)-phenyl]-pentane-1,4-dione (1.040g, 3.01mmol), ethyl-3-aminobenzoate (0.54ml, 3.62mmol) and pTSA (50mg) were heated in toluene (30ml, 0.1M) at reflux for 4 hours. Upon cooling, the mixture was diluted with EtOAc and washed with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography with hexane containing EtOAc (5%) as eluant, to give the desired compound (811mg, 55%).
^{1}H NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7Hz), 2.15 (3H, s), 4.28 (2H, q, J=7Hz), 4.71 (2H, s), 6.13 (1H, d, J=3.5Hz), 6.31 (1H, d, J=3.5Hz), 6.49 (1H, d, J=9Hz), 6.99-7.16 (2H,

m), 7.10-7.15 (1H, m), 7.17 (1H, d, J=3Hz, J=9Hz), 7.22-7.32 (4H, m's excess), 7.38 (1H, d, J=3Hz), 7.73 (1H, s), 7.91 (1H, d, J=8Hz).

d) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



The ethyl ester derivative (144.6mg, 0.30mmol) was heated in a mixture of EtOH (3ml) and 2M NaOH (1.5ml) at reflux in a reacti-vial for 3 hours. Upon cooling, the mixture was diluted with EtOAc, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (136.7mg, 100%).

^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.72 (2H, s), 6.14 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.51 (1H, d, J=9Hz), 7.00-7.08 (2H, m), 7.13-7.21 (2H, m), 7.22-7.36 (4H, m's excess), 7.39 (1H, d, J=2Hz), 7.79 (1H, s), 7.96 (1H, d, J=8Hz).

LC/MS t= 3.99 min [MH+] 462 and 463, [MH-] 460 and 461.

Example 4: 3-{2-[5-Phenyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

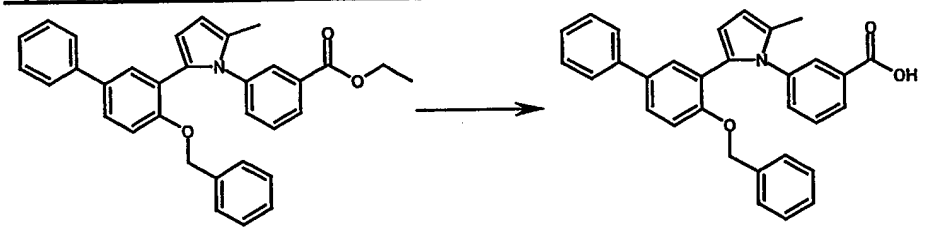
a) 3-{2-[5-Phenyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (109.9mg, 0.21mmol), benzene boronic acid (52mg, 0.43mmol), K_2CO_3 (230mg, 1.67mmol) and tetrakistriphenylphophine palladium (0) (26.0mg, 0.02mmol) were heated in a toulene (1ml) and EtOH (1ml) at 90°C in a reacti-vial for 6 hours. Upon cooling, the mixture was diluted with EtOAc and washed with H_2O, dried (Na_2SO_4), filtered and concentrated. the residue was purified by chromatography, with *iso*-hexane containing a gradient of EtOAc (1.5-5%) to give the title compound (63.4mg, 58%).

^{1}H NMR (400MHz, $CDCl_3$) 1.27 (3H, q, J=7Hz), 2.18 (3H, s), 4.27 (2H, q, J=7Hz), 4.84 (2H, s), 6.16 (1H, d, J=3Hz), 6.40 (1H, d, J=3Hz), 6.72 (1H, d, J=9Hz), 7.10-7.15 (2H, m), 7.17-7.42 (11H, m's excess), 7.47 (1H, d, J=2Hz), 7.82 (1H, s), 7.92 (1H, d, J=8Hz).

LC/MS t=4.31 min [MH+] 488.

b) 3-{2-[5-Phenyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Phenyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (62.1mg, 0.13mmol) was heated in a mixture of EtOH (1.2ml) and 2M NaOH (0.6ml) at 90°C in a reacti-vial for 2 hours. Upon cooling, the mixture was diluted with EtOAc,

washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (58.3mg, 100%).
^{1}H NMR (400MHz, $CDCl_3$) 2.19 (3H, s), 4.83 (2H, s), 6.17 (1H, d, J=3Hz), 6.40 (1H, d, J=3Hz), 6.74 (1H, d, J=8Hz), 7.12 (1H, d, J=8Hz), 7.20-7.45 (12H, m's excess), 7.48 (1H, d, J=2Hz), 7.86 (1H, t, J=3Hz), 7.96 (1H, d, J=8Hz).
LC/MS t= 4.08 min [MH+] 460, [MH-] 458.

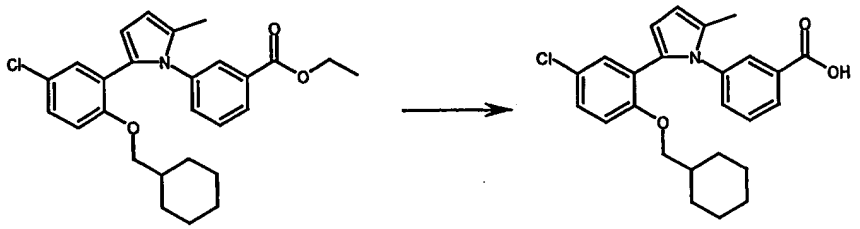
Example 5: 3-{2-[5-Chloro-2-(cyclohexylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 5-Chloro-2-cyclohexylmethoxy-benzaldehyde
5-Chlorosalicylaldehyde (5.025g, 32.08mmol), cyclohexylmethyl bromide (4.70ml, 33.70mmol) and K_2CO_3 (8.890g, 64.42mmol) were heated in DMF (32ml) at 60°C for 18hrs. Upon cooling to room temperature, Et_2O and H_2O were added. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the title compound (6.115g, 85%).
^{1}H NMR (400MHz, $CDCl_3$) 1.12-1.39 (5H, m), 1.66-1.92 (6H, m), 3.85 (2H, d, J=6Hz), 6.92 (1H, d, J=9Hz), 7.46 (1H, dd, J=3Hz, J=9Hz), 7.78 (1H, d, J=3Hz), 10.47 (1H, s).

b) 1-[5-Chloro-2-(cyclohexylmethoxy)-phenyl]-pentane-1,4-dione
A mixture of 2-benzyloxy-5-bromo-benzaldehyde (2.003g, 7.93mmol), methyl vinyl ketone (0.80ml, 9.62mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (307mg, 1.22mmol, 0.15eq) and triethylamine (1.65ml, 11.86mmol) was heated in ethanol (2.4ml, 3M) at reflux for 5 hours. Upon cooling, the mixture was diluted with EtOAc and washed with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4) filtered and concentrated. The residue was purified by chromatography with *iso*-hexane containg a gradient of EtOAc (5-10%) to give the title compound as an oil (1.2153g, 48%).
^{1}H NMR (400MHz, $CDCl_3$) F2944 1.02-1.39 (5H, m), 1.61-1.95 (6H, m), 2.26 (3H, s), 2.85 (2H, t, J=6Hz), 3.27 (2H, t, J=6Hz), 3.84 (2H, d, J=6Hz), 6.88 (1H, d, J=9Hz), 7.37 (1H, dd, J=3Hz, J=9Hz), 7.70 (1H, d, J=3Hz).

c) 3-{2-[5-Chloro-2-(cyclohexylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester
1-[5-Chloro-2-(cyclohexylmethoxy)-phenyl]-pentane-1,4-dione (478.9mg, 1.49mmol), ethyl-3-aminobenzoate (0.27ml, 1.81mmol) and pTSA (25mg) were heated in toluene (15ml, 0.1M) at reflux for 3 hours. Upon cooling, the mixture was diluted with EtOAc and washed with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, with hexane containing a gradient of EtOAc (1-2%) as eluant, to give the desired compound (547mg, 81%).
^{1}H NMR (400MHz, $CDCl_3$) 0.76-0.93 (2H, m), 1.06-1.30 (3H, m's excess), 1.37 (3H, t, J=7Hz), 1.52-1.75 (6H, m's excess), 2.19 (3H, s), 3.40 (2H, d, J=6Hz), 4.35 (2H, q, J=7Hz), 6.11 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.59 (1H, d, J=9Hz), 7.05 (1H, dd, J=3Hz, J=9Hz), 7.09 (1H, d, J=3Hz), 7.17 (1H, d, J=8Hz), 7.31 (1H, t, J=8Hz), 7.83 (1H, s), 7.91 (1H, d, J=8Hz).

d) 3-{2-[5-Chloro-2-(cyclohexylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

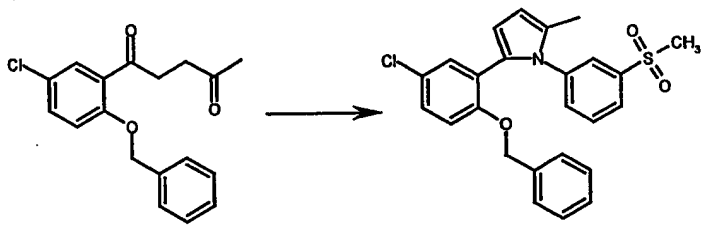


3-{2-[5-Chloro-2-(cyclohexylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (149.0mg, 0.33mmol) was heated in a mixture of EtOH (3ml) and 2M NaOH (1.5ml) at 90°C in a reacti-vial for 2 hours. Upon cooling, the mixture was diluted with EtOAc, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound.
^{1}H NMR (400MHz, $CDCl_3$) 0.78-0.93 (2H, m), 1.06-1.31 (3H, m's excess), 1.54-1.74 (6H, m's excess), 2.19 (3H, s), 3.42 (2H, d, J=6Hz), 6.12 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.60 (1H, d, J=8Hz), 7.06 (1H, dd, J=3Hz, J=8Hz), 7.10 1H, d, J=3Hz), 7.22 (1H, d, J=8Hz), 7.35 (1H, t, J=8Hz), 7.92 (1H, s), 7.97 (1H, d, J=8Hz).
LC/MS t= 4.08, [MH+] 424 and 426, [MH-] 422 and 424.

Example 6: 4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-methanesulfonyl benzene

1-[5-Chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione (251mg, 0.83mmol), 4-methylsulfonylaniline hydrochloride (209mg, 1.01mmol) and triethylamine (0.11ml, 0.79mmol) were heated in toluene (8.3ml, 0.1M) at reflux for 4 hours. Upon cooling, the mixture was diluted with EtOAc and washed with 2 M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, with hexane containing a gradient of EtOAc (10-25%) as eluant, to give the desired compound (188mg, 50%).
^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 3.05 (3H, s), 4.66 (2H, s), 6.15 (1H, s, J=3Hz), 6.34 (1H, d, J=3Hz), 6.60 (1H, d, J=9Hz), 7.01-7.13 (5H, m), 7.23 (1H, d, J=2Hz), 7.28-7.36 (3H, m), 7.74 (2H, d, J=9Hz).
LC/MS t=3.88 min, [MH+] 452 and 454.

Example 7: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-methanesulfonyl benzene



1-[5-chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione (279mg, 0.93mmol), 3-methylsulfonylaniline hydrochloride (262mg, 1.26mmol) and triethylamine (0.12ml, 0.86mmol) were heated in toluene (9.3ml, 0.1M) at reflux for 4.5 hours. Upon cooling, the mixture was diluted with EtOAc and washed with 2M HCl and saturated $NaHCO_3$, dried

(Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, with hexane containing a gradient of EtOAc (10-30%) as eluant, to give the desired compound (270mg, 64%).

^{1}H NMR (400MHz, $CDCl_3$) 2.19 (2H, m), 2.66 (3H, s), 4.75 (2H, s), 6.15 (1H, d, J=3Hz), 6.34 (1H, d, J=3Hz), 6.57 (1H, d, J=9Hz), 6.95-7.10 (3H, m), 7.17-7.34 (5H, m's excess), 7.42 (1H, t, J=8Hz), 7.55 (1H, s), 7.79 (1H, d, J=8Hz).

LC/MS t=3.86 min [MH+] 452 and 454.

Example 8: 3-{2-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 5-Bromo-2-(4-methoxy-benzyloxy)-benzaldehyde

5-Bromo-2-hydroxybenzaldehyde (8.56 g, 0.043 mol, 1 eq) was added to DMF (60 ml). K_2CO_3 (11.75 g, 0.085 mol, 2 eq) and 4-methoxybenzyl chloride (10 g, 0.06 mol, 1.5eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to 60 °C. After 3 hours the reaction had gone to completion. The reaction mixture was quenched with water (250 ml) and washed with EtOAc (2 x 250 ml). The organic extracts were combined and washed with brine (150 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield title compound (13.9 g, 0.04 mol, 100%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) 3.82 (3H, s), 5.10 (2H, s), 6.93 (2H, d, J=8.2Hz), 6.96 (1H, d, J=9.0Hz), 7.34 (2H, d, J=8.2Hz), 7.60 (1H, dd, J=2.2, 8.8Hz), 7.92 (1H, d, J=2.2Hz), 10.5 (1H, s).

LC/MS t = 3.62 min [M+NH_4^+] 337.9.

b) 1-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-pentane-1,4-dione

5-Bromo-2-(4-methoxy-benzyloxy)-benzaldehyde (9.45 g, 0.029 mol, 1 eq) was added to EtOH (9 ml). TEA (12.25 ml, 0.088 mol, 3 eq), methyl vinyl ketone (2.10 g, 0.03 mol, 1.02 eq) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (2.22 g, 8.80 mmol, 0.3 eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to reflux. After 18 hours the reaction had gone to completion. The reaction mixture was quenched with saturated NH_4Cl solution (300 ml) and washed with EtOAc (2 x 250 ml). The organic extracts were combined and washed with saturated $NaHCO_3$ solution (250 ml) and brine (200 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield a dark oil. The crude product was purified by chromatography on silica gel (20% EtOAc/*iso*-hexane) to yield title compound (6.42 g, 0.016 mol, 57 %) as a yellow oil which crystallised to form a yellow solid upon cooling.

^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 2.76 (2H, t, J=6.0Hz), 3.19 (2H, t, J=6.0Hz), 3.82 (3H, s), 5.08 (2H, s), 6.91 (3H, m), 7.34 (2H, d, J=8.2Hz), 7.51 (1H, dd, J=2.2, 8.4Hz), 7.82 (1H, d, J=2.2Hz).

LC/MS t = 3.55 mins [PMB^+] 121.

c) 3-{2-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

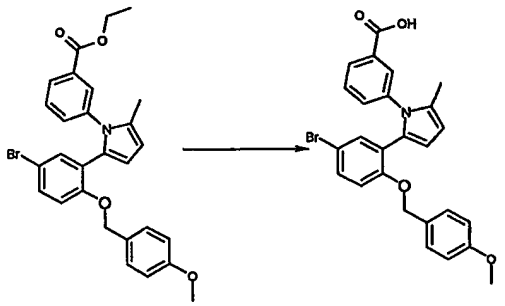
1-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-pentane-1,4-dione (8.017 g, 0.02 mol, 1 eq) and ethyl-3-aminobenzoate (3.67 ml, 0.025 mol, 1.2 eq) were combined in toluene (3 ml).

After complete addition the vessel was heated to reflux. After 12 hours the reaction had gone to completion. The remaining solvent was removed *in vacuo* to yield a dark oil. The crude product was purified by chromatography on silica gel (11% EtOAc:*iso*-hexane) to yield title compound (6.252 g, 0.012 mol, 60 %) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) 1.31 (3H t,, J=7.0Hz), 2.14 (3H, s), 3.79 (3H, s), 4.29 (2H, q, J =7.0Hz), 4.63 (2H, s), 6.12 (1H, d, J=3.0Hz), 6.29 (1H, d, J=3.3Hz), 6.51 (1H, d, J=8.4Hz), 6.81 (2H, d, J=8.6Hz), 6.98 (2H, d, J=8.2Hz), 7.11 (1H, br d, J=8.0Hz), 7.17 (1H, dd, J=2.2, 8.4Hz), 7.28 (1H, t, J=7.6Hz), 7.37 (1H, d, J=2.2Hz), 7.72 (1H, t, J=1.5Hz), 7.91 (1H, br d, J=7.8Hz).

LC/MS t = 4.22 mins [MH^+] 519.9.

d) 3-{2-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (150 mg, 0.29 mmol, 1 eq) was added to EtOH (3 ml) and 2M NaOH (1.5 ml) in a reacti-vial. The vessel was heated to 100 °C. After 2 hours the reaction had gone to completion. The reaction mixture was quenched with 2M HCl solution (10 ml) and washed with EtOAc (2 x 10 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield the title compound (131 mg, 0.27 mmol, 92 %) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) 2.14 (3H, s), 3.78 (3H, s), 4.64 (2H, s), 6.12 (1H, d, J=3.0Hz), 6.30 (1H, d, J=3.0Hz), 6.54 (1H, d, J=8.2Hz), 6.81 (2H, d, J=8.2Hz), 6.99 (2H, d, J=8.2Hz), 7.15 (1H, br d, J=8.0Hz), 7.18 (1H, dd, J=2.0, 8.6Hz), 7.30 (1H, t, J=7.8Hz), 7.36 (1H, d, J=2.0Hz), 7.77 (1H, br s), 7.95 (1H, br d, J=7.9Hz).

LC/MS t = 3.95 mins [MH^+] 492.

Example 9: 3-{2-[5-Bromo-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

A solution of 3-{2-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester. (5.95 g, 0.011 mol, 1 eq) in 4.0 M HCl in dioxane (30 ml) was stirred for 30 minutes at room temperature under N_2. After this time the reaction had gone to completion and the solvent was removed *in vacuo* to yield the crude product as a dark oil. The crude product was purified by chromatography on silica gel (10%EtOAc:*iso*-hexane) to yield title compound (817 mg, 2.04 mmol, 18%) as an orange oil.

^{1}H NMR (400MHz, $CDCl_3$) 1.38 (3H, t, J=7.0Hz), 2.16 (3H, s), 4.36 (2H, q, J=7.0Hz), 5.97 (1H, s), 6.15 (1H, d, J=3.6Hz), 6.35 (1H, d, J=3.6Hz), 6.73 (1H, d, J=8.4Hz), 6.89 (1H, d, J=2.2Hz), 7.15 (1H, dd, J=2.0, 8.2Hz), 7.22 (1H, br d), 7.39 (1H, t, J=7.8Hz), 7.81 (1H, t, J=1.5Hz), 7.99 (1H, br d, J=7.8Hz).

LC/MS t = 3.79 mins [MH^+] 400.

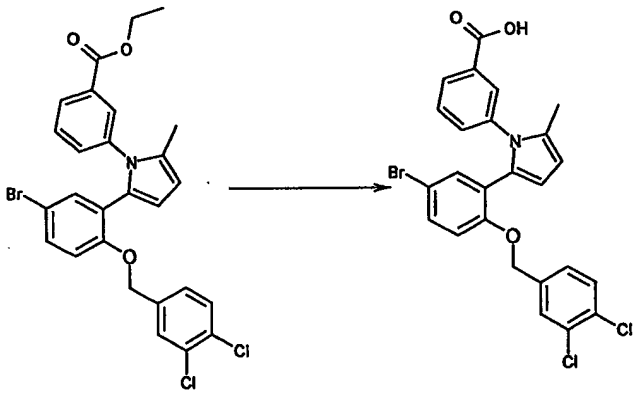
b) 3-{2-[5-Bromo-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (130 mg, 0.33 mmol, 1 eq) was added to DMF (1.3 ml). K_2CO_3 (92 mg, 0.66 mmol, 2 eq) and 3,4-dichlorobenzyl bromide (85.7 µL, 0.5 mmol, 1.5eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to 60 °C. After 3 hours the reaction had gone to completion. The reaction mixture was quenched with water (20 ml) and washed with EtOAc (2 x 20 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo*. The crude product was purified by chromatography on silica gel (3% EtOAc:*iso*-hexane) to yield title compound (104 mg, 0.19 mmol, 57%) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7.1Hz), 2.18 (3H, s), 4.29 (2H, q, J=7.0Hz), 4.63 (2H, s), 6.15 (1H, d, J=3.2Hz), 6.30 (1H, d, J=3.3Hz), 6.46 (1H, d, J=8.8Hz), 6.87 (1H, dd, J=1.8, 8.0Hz), 7.12 (1H, br s), 7.13 (1H, br d, J=7.0Hz), 7.20 (1H, dd, J=2.0, 8.2Hz), 7.30 (1H, t, J=8.0Hz), 7.35 (1H, d, J=8.0Hz), 7.42 (1H, d, J=2.0Hz), 7.72 (1H, t, J=1.2Hz), 7.91 (1H, br d, J=7.8Hz).

LC/MS t = 4.48 mins [MH^+] 558

c) 3-{2-[5-Bromo-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Bromo-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (100 mg, 0.18 mmol, 1 eq) was added to EtOH (2 ml) and 2M NaOH (1 ml) in a reactivial. The vessel was heated to reflux. After 2 hours the reaction had gone to completion. The reaction mixture was quenched with 2M HCl solution (10 ml) and washed with EtOAc (2 x 10 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield the title compound (86 mg, 0.27 mmol, 91 %) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.65 (2H, s), 6.16 (1H, d, J=3.2Hz), 6.31 (1H, d, J=3.4Hz), 6.48 (1H, d, J=8.8Hz), 6.89 (1H, dd, J=1.8, 8.1Hz), 7.14 (1H, d, J=1.8Hz), 7.17

(1H, br d, J=8.0Hz), 7.21 (1H, dd, J=2.0, 8.4Hz), 7.34 (1H, t, J=7.8Hz), 7.35 (1H, d, J=8.0Hz), 7.42 (1H, d, J=2.0Hz), 7.77 (1H, br s), 7.98 (1H, br d, J=7.8Hz).
LC/MS t = 4.28 mins [MH^+] 530.

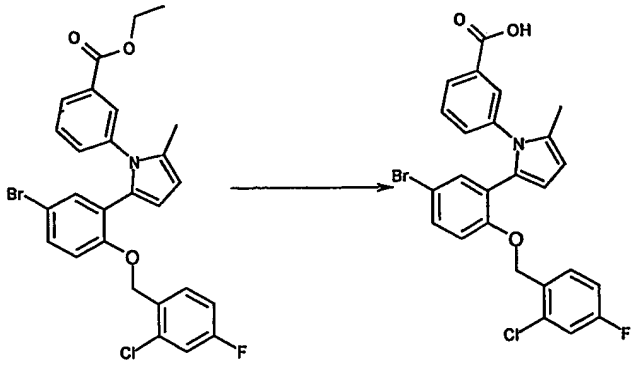
Example 10: 3-{2-[5-Bromo-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (130 mg, 0.33 mmol, 1 eq) was added to DMF (1.3 ml). K_2CO_3 (92 mg, 0.66 mmol, 2 eq) and 2-chloro-4-fluorobenzyl bromide (111.74 mg, 0.5 mmol, 1.5eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to 60 °C. After 3 hours the reaction had gone to completion. The reaction mixture was quenched with water (20 ml) and washed with EtOAc (2 x 20 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo*. The crude product purified by chromatography on silica gel (3% EtOAc:*iso*-hexane) to yield title compound (122 mg, 67%) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7.0Hz), 2.17 (3H, s), 4.29 (2H, q, J=7.0Hz), 4.73 (2H, s), 6.14 (1H, d, J=3.2Hz), 6.31 (1H, d, J=3.6Hz), 6.47 (1H, d, J=8.4Hz), 6.89 (2H, m), 7.09 (1H, dd, J=1.6, 8.0Hz), 7.14 (1H, br d, J=7.6Hz), 7.20 (1H, dd, J=2.4, 8.5Hz), 7.31 (1H, t, J=7.8Hz), 7.40 (1H, d, J=2.0Hz), 7.73 (1H, t, J=1.4Hz), 7.92 (1H, br d, J=7.8Hz).
LC/MS t = 4.39 mins [MH^+] 541.9.

b) 3-{2-[5-Bromo-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Bromo-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (100 mg, 0.18 mmol, 1 eq) was added to EtOH (2 ml) and 2M NaOH (1 ml) in a reactivial. The vessel was heated to 100 °C. After 2 hours the reaction had gone to completion. The reaction mixture was quenched with 2M HCl solution (10 ml) and washed with EtOAc (2 x 10 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield the title compound (95 mg, 100 %) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.74 (2H, s), 6.15 (1H, d, J=3.0Hz), 6.31 (1H, d, J=3.0Hz), 6.50 (1H, d, J=8.4Hz), 6.91 (2H, m), 7.07 (1H, dd, J= 2.0, 8.0Hz), 7.21 (2H, m),

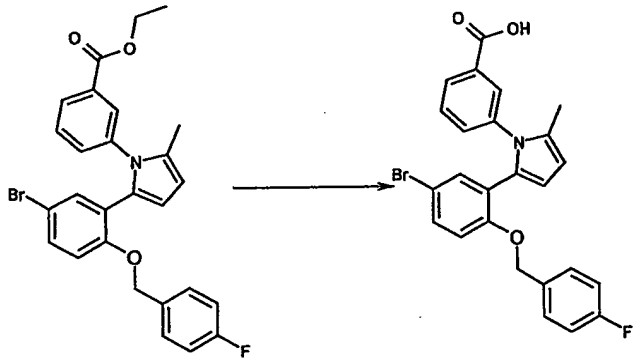
7.34 (1H, t, J=7.8Hz), 7.39 (1H, d, J=2.0Hz), 7.79 (1H, t, J=1.8Hz), 7.98 (1H, br d, J=7.8Hz).
LC/MS t = 4.16 mins [MH^+] 513.8.

Example 11: 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (130 mg, 0.33 mmol, 1 eq) was added to DMF (1.3 ml). K_2CO_3 (92 mg, 0.66 mmol, 2 eq) and 4-fluorobenzyl bromide (61.8 µL, 0.5 mmol, 1.5eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to 60 °C. After 3 hours the reaction had gone to completion. The reaction mixture was quenched with water (20 ml) and washed with EtOAc (2 x 20 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo*. The crude product was purified by chromatography on silica gel (7% EtOAc:*iso*-hexane) to yield title compound (114 mg, 69%) as a colourless oil.
^1H NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7.0Hz), 2.16 (3H, s), 4.29 (2H, q, J=7.0Hz), 4.72 (2H, s), 6.13 (1H, d, J=3.2Hz), 6.29 (1H, d, J=3.2Hz), 6.48 (1H, d, J=8.4Hz), 6.98 (4H, m), 7.10 (1H, br d, J=7.8Hz), 7.19 (1H, dd, J=2.0, 8.7Hz), 7.28 (1H, t, J=7.8Hz), 7.39 (1H, d, J=2.4Hz), 7.70 (1H, br s), 7.90 (1H, br d, J=7.6Hz).
LC/MS t = 4.25 mins [MH^+] 508.0.

b) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (100 mg, 0.20 mmol, 1 eq) was added to EtOH (2 ml) and 2M NaOH (1 ml) in a reacti-vial. The vessel was heated to 100 °C. After 2 hours the reaction had gone to completion. The reaction mixture was quenched with 2M HCl solution (10 ml) and washed with EtOAc (2 x 10 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield the title compound (91 mg, 96 %) as a yellow oil.
^1H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.68 (2H, s), 6.13 (1H, dd, J=0.2, 3.0Hz), 6.30 (1H, d, J=3.0Hz), 6.52 (1H, d, J=8.4Hz), 6.96 (2H, br t, J=8.2Hz), 7.02 (2H, dd, J=7.0, 8.2Hz), 7.15 (1H, br d, J=8.0Hz), 7.20 (1H, dd, J=2.2, 8.4Hz), 7.31 (1H, t, J=7.8Hz), 7.38 (1H, d, J=2.2Hz), 7.76 (1H, t, J=1.6Hz), 7.97 (1H, br d, J=7.6Hz).

LC/MS t = 3.98 mins [MH^+] 479.9

Example 12: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

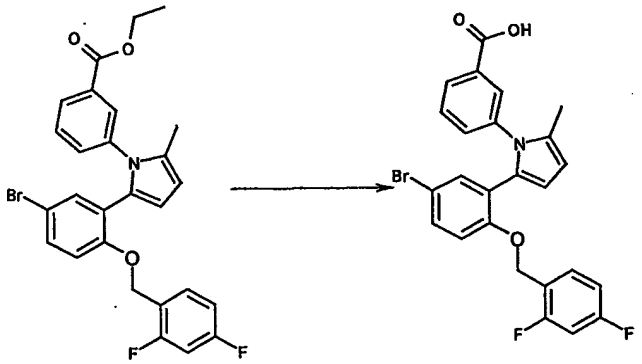
a) 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (130 mg, 0.33 mmol, 1 eq) was added to DMF (1.3 ml). K_2CO_3 (92 mg, 0.66 mmol, 2 eq) and 2,4-difluorobenzyl bromide (69.0 µL, 0.5 mmol, 1.5eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to 60 °C. After 3 hours the reaction had gone to completion. The reaction mixture was quenched with water (20 ml) and washed with EtOAc (2 x 20 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo*. The crude product was purified by chromatography on silica gel (7% EtOAc:*iso*-hexane) to yield title compound (116 mg, 67%) as a colourless oil.

^1H NMR (400MHz, $CDCl_3$) 1.32 (3H, t, J=7.0Hz), 2.15 (3H, s), 4.30 (2H, q, J=7.0Hz), 4.72 (2H, s), 6.12 (1H, d, J=3.2Hz), 6.29 (1H, d, J=3.4Hz), 6.53 (1H, d, J=8.4Hz), 6.78 (2H, m), 6.95 (1H, dt, J=6.4, 9.0Hz), 7.12 (1H, br d, J=8.0Hz), 7.21 (1H, dd, J =2.2, 8.8Hz), 7.29 (1H, t, J=7.7Hz), 7.37 (1H, d, J=2.4Hz), 7.72 (1H, br s), 7.90 (1H, br d, J=7.9Hz).

LC/MS t = 4.27 mins [MH^+] 525.9.

b) 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (100 mg, 0.20 mmol, 1 eq) was added to EtOH (2 ml) and 2M NaOH (1 ml) in a reacti-vial. The vessel was heated to 100°C. After 2 hours the reaction had gone to completion. The reaction mixture was quenched with 2M HCl solution (10 ml) and washed with EtOAc (2 x 10 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield the title compound (85 mg, 90 %) as a yellow oil.

^1H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.73 (2H, s), 6.13 (1H, d, J=3.0Hz), 6.30 (1H, d, J=3.0Hz), 6.56 (1H, d, J=8.4Hz), 6.79 (2H, m), 6.99 (1H, q, J=7.8Hz), 7.17 (1H, br d, J=8.0Hz), 7.22 (1H, dd, J=2.2, 8.6Hz), 7.34 (1H, t, J=8.0Hz), 7.37 (1H, d, J=2.2Hz), 7.78 (1H, br s), 7.98 (1H, br d, J=7.7Hz).

LC/MS t = 4.01 mins [MH^+] 497.9.

Example 13: 3-{2-[5-Bromo-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (130 mg, 0.33 mmol, 1 eq) was added to DMF (1.3 ml). K_2CO_3 (92 mg, 0.66 mmol, 2 eq) and 4-chlorobenzyl bromide (102.7 mg, 0.5 mmol, 1.5eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to 60 °C. After 3 hours the reaction had gone to completion. The reaction mixture was quenched with water (20 ml) and washed with EtOAc (2 x 20 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo*. The crude product was purified by chromatography on silica gel (7% EtOAc:*iso*-hexane) to yield title compound (126 mg, 74%) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$) 1.32 (3H, t, J=7.0Hz), 2.16 (3H, s), 4.29 (2H, q, J=7.0Hz), 4.66 (2H, s), 6.13 (1H, d, J=3.2Hz), 6.29 (1H, d, J=3.4Hz), 6.47 (1H, d, J=8.2Hz), 6.95 (2H, d, J=8.0Hz), 7.12 (1H, br d, J=7.8Hz), 7.18 (1H, dd, J=2.2, 8.4Hz), 7.24 (2H, d, J=8.0Hz), 7.28 (1H, t, J=7.8Hz), 7.40 (1H, d, J=2.2Hz), 7.71 (1H, br s), 7.91 (1H, br d, J=7.8Hz).
LC/MS t = 4.38 mins [MH^+] 523.9.

b) 3-{2-[5-Bromo-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

3-{2-[5-Bromo-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (100 mg, 0.20 mmol, 1 eq) was added to EtOH (2 ml) and 2M NaOH (1 ml) in a reactivial. The vessel was heated to 100 °C. After 2 hours the reaction had gone to completion. The reaction mixture was quenched with 2M HCl solution (10 ml) and washed with EtOAc (2 x 10 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield the title compound (93 mg, 98 %) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.68 (2H, s), 6.13 (1H, d, J=3.0Hz), 6.30 (1H, d, J=3.2Hz), 6.49 (1H, d, J=8.4Hz), 6.98 (2H, d, J=8.2Hz), 7.16 (1H, br d, J=7.8Hz), 7.19 (1H, dd, J=2.2, 8.4Hz), 7.25 (2H, d, J=8.0Hz), 7.32 (1H, t, J=7.8Hz), 7.39 (1H, d, J=2.2Hz), 7.77 (1H, br s), 7.97 (1H, br d, J=7.8Hz).
LC/MS t = 4.14 mins [MH^+] 495.8.

Example 14: 3-{2-[2-(4-Methoxy-benzyloxy)-phenyl]-pyrrol-1-yl}-benzoic acid

a) 2-(4-Methoxy-benzyloxy)-benzaldehyde

2-Hydroxybenzaldehyde (5.20 g, 0.043 mol, 1 eq) was added to DMF (60 ml). K_2CO_3 (11.75 g, 0.085 mol, 2 eq) and 4-methoxybenzyl chloride (10 g, 0.06 mol, 1.5eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to 60 °C. After 3 hours the reaction had gone to completion. The reaction mixture was quenched with water (250 ml) and washed with EtOAc (2 x 250 ml). The organic extracts were combined and washed with brine (150 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield title compound (13.9 g, 0.04 mol, 100%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) 3.82 (3H, s), 5.12 (2H, s), 6.93 (2H, d, J=8.2Hz), 7.05 (2H, m), 7.36 (2H, d, J=8.2Hz), 7.52 (1H, dt, J=1.8, 8.0Hz), 7.85 (1H, dd, J=1.8, 8.0Hz), 10.5 (1H, s).

LC/MS t = 3.31 mins [PMB^+] 120.9.

b) 1-[2-(4-Methoxy-benzyloxy)-phenyl]-pentane-1,4-dione

2-(4-Methoxy-benzyloxy)-benzaldehyde (2.50 g, 7.23 mmol, 1 eq) was added to EtOH (2.2 ml). Et_3N (1.51 ml, 10.8 mmol, 1.5 eq), methyl vinyl ketone (516.5 mg, 7.38 mmol, 1.02 eq) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (2.22 g, 8.80 mmol, 0.3 eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to reflux. After 24 hours the reaction had gone to completion. The reaction mixture was quenched with saturated NH_4Cl solution (200 ml) and washed with EtOAc (2 x 200 ml). The organic extracts were combined and washed with saturated $NaHCO_3$ solution (150 ml) and brine (150 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield a dark oil. The crude product was purified by chromatography on silica gel (20% EtOAc/*iso*-hexane) to yield title compound (1.27 g, 56 %) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 2.73 (2H, t, J=6.1Hz), 3.23 (2H, t, J=6.1Hz), 3.81 (3H, s), 5.08 (2H, s), 6.91 (2H, d, J=7.0Hz), 7.00 (2H, m), 7.37 (2H, d, J=7.0Hz), 7.42 (1H, dt, J=1.8, 8.0Hz), 7.72 (1H, d, J=1.8, 7.9Hz).

LC/MS t = 3.28 mins [PMB^+] 120.9.

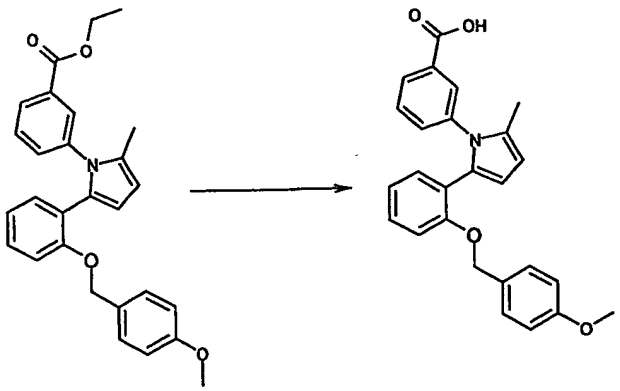
c) 3-{2-[2-(4-Methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

1-[2-(4-Methoxy-benzyloxy)-phenyl]-pentane-1,4-dione (6.76 g, 0.022 mol, 1 eq) and ethyl-3-aminobenzoate (3.88 ml, 0.026 mol, 1.2 eq) were combined in toluene (2.2 ml). After complete addition the vessel was heated to reflux. After 12 hours the reaction had gone to completion. The remaining solvent was removed *in vacuo* to yield a dark oil. The crude product was purified by chromatography on silica gel (11% EtOAc:*iso*-hexane) to yield title compound (5.79 g, 61 %) as a yellow solid.

^{1}H NMR (400MHz, $CDCl_3$) 1.30 (3H, t, J=7.0Hz), 2.16 (3H, s), 3.79 (3H, s), 4.29 (2H, q, J=7.0Hz), 4.71 (2H, s), 6.13 (1H, d, J=3.4Hz), 6.30 (1H, d, J=3.5Hz), 6.68 (1H, d, J=8.0Hz), 6.81 (2H, d, J=8.4Hz), 6.85 (1H, dt, J=0.9, 7.2Hz), 7.03 (2H, d, J=8.2Hz), 7.09 (2H, m), 7.19 (1H, dd, J=1.8, 7.8Hz), 7.23 (1H, t, J=7.8Hz), 7.76 (1H, t, J=1.4Hz), 7.88 (1H, br d, J=7.8Hz).

LC/MS t = 4.04 mins [$M+NH_4^+$] 407.9.

d) 3-{2-[2-(4-Methoxy-benzyloxy)-phenyl]-pyrrol-1-yl}-benzoic acid



3-{2-[2-(4-Methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (150 mg, 0.34 mmol, 1 eq) was added to EtOH (3 ml) and 2M NaOH (1.5 ml) in a reactivial. The vessel was heated to 100 °C. After 2 hours the reaction had gone to completion. The reaction mixture was quenched with 2M HCl solution (10 ml) and washed with EtOAc (2 x 10 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield the title compound (125 mg, 0.27 mmol, 89%) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) 2.16(3H, s), 3.77 (3H, s), 4.70 (2H, s), 6.12 (1H, d, J=3.3Hz), 6.30 (1H, d, J=3.3Hz), 6.69 (1H, d, J=8.0Hz), 6.82 (2H, d, J=8.2Hz), 6.86 (1H, t, J=7.6Hz), 7.03 (2H, d, J=8.2Hz), 7.10 (1H, dt, J=1.6, 8.0Hz), 7.15 (1H, br d, J=8.0Hz), 7.22 (1H, dd, J=1.6, 7.9Hz), 7.27 (1H, t, J=7.8Hz), 7.77 (1H, br s), 7.92 (1H, br d, J=7.8Hz).

LC/MS t = 3.73 min [MH^+] 414.0.

Example 15: 3-{2-[2-(3,4-Dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[2-(Hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

A solution of 3-{2-[2-(4-Methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester. (3.96 g, 0.009 mol, 1 eq) in 4.0 M HCl in dioxane (20 ml) was stirred for 30 minutes at room temperature under N_2. After this time the reaction had gone to completion and the solvent was removed *in vacuo* to yield the crude product as a dark oil. The crude product was purified by chromatography on silica gel (10%EtOAc:*iso*-hexane) to yield title compound (1.242 g, 45%) as a brown solid.

^{1}H NMR (400MHz, $CDCl_3$) 1.38 (3H, t, J=7.0Hz), 2.16 (3H, s), 4.35 (2H, q, J=7.0Hz), 5.98 (1H, s), 6.17 (1H, d, J=3.8Hz), 6.37 (1H, d, J=3.8Hz), 6.61 (1H, dt, J=1.0, 7.8Hz), 6.71 (1H, dd, J=1.6, 7.8Hz), 6.88 (1H, dd, J=1.0, 8.0Hz), 7.16 (1H, dt, J=1.8, 8.0Hz), 7.18 (1H, br d), 7.35 (1H, t, J=7.8Hz), 7.83 (1H, t, J=1.5Hz), 7.94 (1H, br d, J=7.8Hz).

LC/MS t = 3.54 mins [MH^+] 322.1.

b) 3-{2-[2-(3,4-Dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

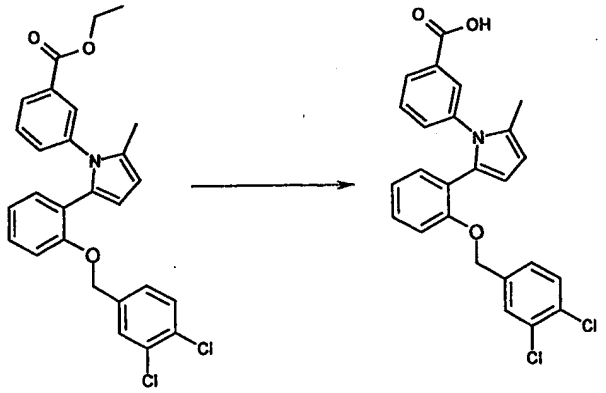
3-{2-[2-(Hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200 mg, 0.62 mmol, 1 eq) was added to DMF (2 ml). K_2CO_3 (172 mg, 1.25 mmol, 2 eq) and 3,4-dichlorobenzyl bromide (160.2 µL, 0.93 mmol, 1.5eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to 60 °C. After 3 hours the reaction

had gone to completion. The reaction mixture was quenched with water (20 ml) and washed with EtOAc (2 x 20 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo*. The crude product was purified by chromatography on silica gel (5% EtOAc:*iso*-hexane) to yield title compound (225 mg, 75%) as a colourless oil.

^1H NMR (400MHz, $CDCl_3$) 1.30 (3H, t, J=7.1Hz), 2.18 (3H, s), 4.28 (2H, q, J=7.0Hz), 4.70 (2H, s), 6.16 (1H, d, J=3.2Hz), 6.30 (1H, d, J=3.0Hz), 6.60 (1H, d, J=8.2Hz), 6.90 (2H, m), 7.11 (2H, m), 7.18 (1H, d, J=1.6Hz), 7.26 (2H, m), 7.35 (1H, d, J=8.0Hz), 7.74 (1H, br s), 7.88 (1H, br d, J=7.8Hz).

LC/MS t = 4.32 mins [MH^+] 480.0.

c) 3-{2-[2-(3,4-Dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[2-(3,4-Dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (150 mg, 0.31 mmol, 1 eq) was added to EtOH (3 ml) and 2M NaOH (1.5 ml) in a reactivial. The vessel was heated to 100 °C. After 2 hours the reaction had gone to completion. The reaction mixture was quenched with 2M HCl solution (10 ml) and washed with EtOAc (2 x 10 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield the title compound (140 mg, 99%) as a yellow oil.

^1H NMR (400MHz, $CDCl_3$) 2.19 (3H, s), 4.70 (2H, s), 6.17 (1H, d, J=3.0Hz), 6.30 (1H, d, J=3.0Hz), 6.61 (1H, d, J=8.0Hz), 6.91 (2H, m), 7.13 (2H, m), 7.18 (1H, d, J=1.4Hz), 7.28 (2H, m), 7.35 (1H, d, J=8.0Hz), 7.78 (1H, br s), 7.94 (1H, br d, J=7.8Hz).

LC/MS t = 4.32 mins [MH^+] 451.9.

<u>Example 16: 3-{2-[2-(2-Chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid</u>

a) 3-{2-[2-(2-Chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

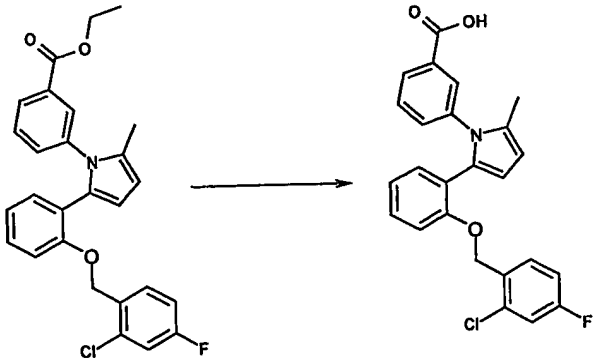
3-{2-[2-(Hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200 mg, 0.62 mmol, 1 eq) was added to DMF (2 ml). K_2CO_3 (172 mg, 1.25 mmol, 2 eq) and 2-chloro-4-fluorobenzyl bromide (208.9 mg, 0.93 mmol, 1.5eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to 60 °C. After 3 hours the reaction had gone to completion. The reaction mixture was quenched with water (20 ml) and washed with EtOAc (2 x 20 ml). The organic extracts were combined and washed with

brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo*. The crude product was purified by chromatography on silica gel (5% EtOAc:*iso*-hexane) to yield title compound (189 mg, 65%) as a colourless oil.

^1H NMR (400MHz, $CDCl_3$) 1.30 (3H, t, J=7.1Hz), 2.18 (3H, s), 4.28 (2H, q, J=7.0Hz), 4.79 (2H, s), 6.15 (1H, d, J=3.4Hz), 6.31 (1H, d, J=3.4Hz), 6.61 (1H, d, J=8.0Hz), 6.88 (2H, m), 6.98 (1H, dd, J=7.0, 8.2Hz), 7.08 (1H, dd, J=2.0, 8.0Hz), 7.12 (2H, m), 7.26 (2H, m), 7.77 (1H, br s), 7.89 (1H, br d, J=7.6Hz).

LC/MS t = 4.23 mins $[MH^+]$ 464.0.

b) 3-{2-[2-(2-Chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[2-(2-Chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (150 mg, 0.32 mmol, 1 eq) was added to EtOH (3 ml) and 2M NaOH (1.5 ml) in a reacti-vial. The vessel was heated to 100 °C. After 2 hours the reaction had gone to completion. The reaction mixture was quenched with 2M HCl solution (10 ml) and washed with EtOAc (2 x 10 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield the title compound (126 mg, 89%) as a yellow oil.

^1H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.79 (2H, s), 6.16 (1H, d, J=3.4Hz), 6.32 (1H, d, J=3.4Hz), 6.64 (1H, d, J=8.2Hz), 6.90 (2H, m), 7.00 (1H, dd, J=7.0, 8.2Hz), 7.06 (1H, dd, J=2.2, 8.0Hz), 7.13 (1H, dt, J=1.6, 7.8Hz), 7.20 (1H, br d, J=8.0Hz), 7.25 (1H, dd, J=1.4, 8.0Hz), 7.30 (1H, t, J=7.8Hz), 7.79 (1H, br s), 7.95 (1H, br d, J=7.8Hz).

LC/MS t = 3.96 mins $[MH^+]$ 436.0.

<u>Example 17: 3-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid</u>

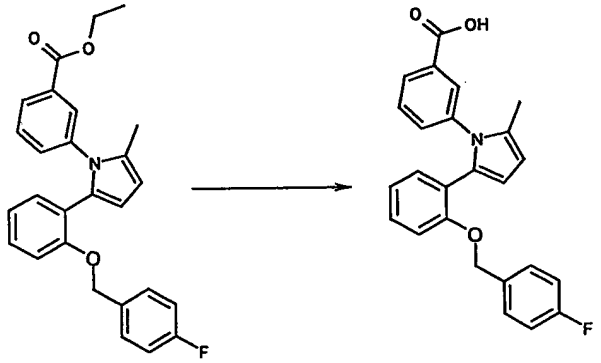
a) 3-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[2-(Hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200 mg, 0.62 mmol, 1 eq) was added to DMF (2 ml). K_2CO_3 (172 mg, 1.25 mmol, 2 eq) and 4-fluorobenzyl bromide (115.4 µL, 0.93 mmol, 1.5eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to 60 °C. After 3 hours the reaction had gone to completion. The reaction mixture was quenched with water (20 ml) and washed with EtOAc (2 x 20 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo*. The crude product was purified by chromatography on silica gel (5% EtOAc:*iso*-hexane) to yield title compound (175 mg, 65%) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$) 1.30 (3H, t, J=7.0Hz), 2.16 (3H, s), 4.28 (2H, q, J=7.0Hz), 4.72 (2H, s), 6.13 (1H, d, J=3.0Hz), 6.30 (1H, d, J=3.0Hz), 6.64 (1H, d, J=8.2Hz), 6.86 (1H, dt, J=0.4, 7.4Hz), 6.97 (2H, t, J=8.2Hz), 7.08 (4H, m), 7.23 (2H, m), 7.72 (1H, t, J=1.8Hz), 7.88 (1H, br d, J=7.8Hz).

LC/MS t = 4.07 mins [MH^+] 430.1.

b) 3-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (150 mg, 0.35 mmol, 1 eq) was added to EtOH (3 ml) and 2M NaOH (1.5 ml) in a reacti-vial. The vessel was heated to 100 °C. After 2 hours the reaction had gone to completion. The reaction mixture was quenched with 2M HCl solution (10 ml) and washed with EtOAc (2 x 10 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield the title compound (121 mg, 86%) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.72 (2H, s), 6.15 (1H, d, J=3.2Hz), 6.30 (1H, d, J=3.0Hz), 6.66 (1H, d, J=8.0Hz), 6.88 (1H, br d, J=7.6Hz), 6.97 (2H, dd, J=8.0, 9.6Hz), 7.10 (4H, m), 7.26 (2H, m), 7.77 (1H, t, J=1.6Hz), 7.93 (1H, br d, J=7.8Hz).
LC/MS t = 3.77 mins [MH^+] 402.1.

<u>Example 18: 3-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid</u>

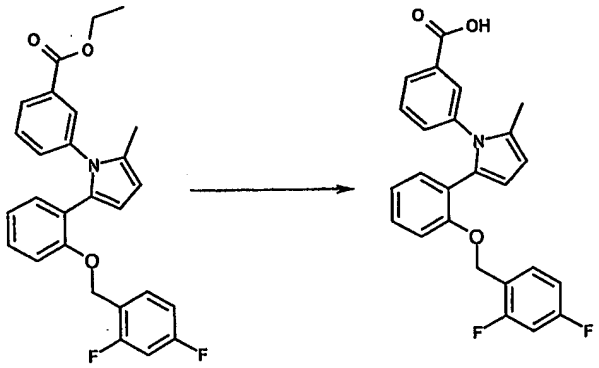
a) 3-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[2-(Hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200 mg, 0.62 mmol, 1 eq) was added to DMF (2 ml). K_2CO_3 (172 mg, 1.25 mmol, 2 eq) and 2,4-difluorobenzyl bromide (129.0 µL, 0.93 mmol, 1.5eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to 60 °C. After 3 hours the reaction had gone to completion. The reaction mixture was quenched with water (20 ml) and washed with EtOAc (2 x 20 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo*. The crude product was purified by chromatography on silica gel (3% EtOAc:*iso*-hexane) to yield title compound (183 mg, 66%) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7.0Hz), 2.16 (3H, s), 4.29 (2H, q, J=7.0Hz), 4.79 (2H, s), 6.13 (1H, d, J=3.0Hz), 6.30 (1H, d, J=3.2Hz), 6.68 (1H, d, J=8.0Hz), 6.78 (2H, m),

6.87 (1H, dt, J=0.4, 7.6Hz), 7.02 (1H, dt, J=6.2, 9.0Hz), 7.11 (2H, m), 7.21 (1H, dd, J=1.6, 7.8Hz), 7.25 (1H, t, J=7.8Hz), 7.75 (1H, t, J=1.8Hz), 7.89 (1H, br d, J=7.8Hz).
LC/MS t = 4.10 mins [MH^+] 448.1

b) 3-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



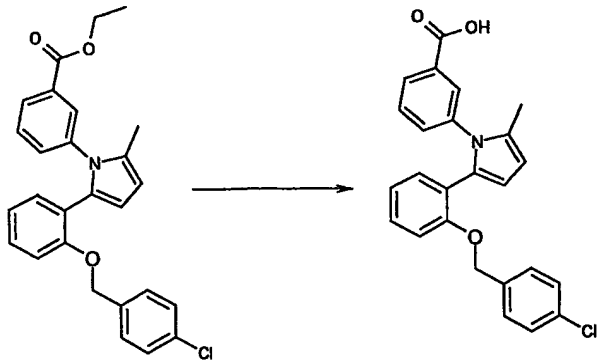
3-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (150 mg, 0.34 mmol, 1 eq) was added to EtOH (3 ml) and 2M NaOH (1.5 ml) in a reacti-vial. The vessel was heated to 100°C. After 2 hours the reaction had gone to completion. The reaction mixture was quenched with 2M HCl solution (10 ml) and washed with EtOAc (2 x 10 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield the title compound (131 mg, 93%) as a yellow oil.
^{1}H NMR (400MHz, *d*6-DMSO) 2.03 (3H, s), 4.87 (2H, s), 6.02 (1H, d, J=3.0Hz), 6.17 (1H, d, J=3.2Hz), 6.80 (1H, br t, J=7.5Hz), 6.91 (1H, d, J=8.0Hz), 7.01 (1H, br d, J=7.0Hz), 7.07 (1H, dt, J=2.0, 8.0Hz), 7.11 (2H, m), 7.25 (2H, m), 7.34 (1H, t, J=7.8Hz), 7.53 (1H, br s), 7.81 (1H, br d, J=7.4Hz).
LC/MS t = 3.80 mins [MH^+] 420.0.

Example 19: 3-{2-[2-(4-Chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[2-(4-Chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[2-(Hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200 mg, 0.62 mmol; 1 eq) was added to DMF (2 ml). K_2CO_3 (172 mg, 1.25 mmol, 2 eq) and 4-chlorobenzyl bromide (192.0 mg, 0.93 mmol, 1.5eq) were added to the stirred reaction mixture. After complete addition the vessel was heated to 60 °C. After 3 hours the reaction had gone to completion. The reaction mixture was quenched with water (20 ml) and washed with EtOAc (2 x 20 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo*. The crude product was purified by chromatography on silica gel (3% EtOAc:*iso*-hexane) to yield title compound (179 mg, 64%) as a colourless oil.
^{1}H NMR (400MHz, $CDCl_3$) 1.30 (3H, t, J=7.0Hz), 2.17 (3H, s), 4.28 (2H, q, J=7.0Hz), 4.72 (2H, s), 6.13 (1H, d, J=3.2Hz), 6.30 (1H, d, J=3.0Hz), 6.61 (1H, d, J=7.8Hz), 6.87 (1H, dt, J=0.4, 7.8Hz), 7.00 (2H, d, J=8.2Hz), 7.10 (2H, m), 7.24 (4H, m), 7.74 (1H, t, J=1.8Hz), 7.88 (1H, br d, J=7.8Hz).
LC/MS t = 4.20 mins [MH^+] 446.0.

b) 3-{2-[2-(4-Chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[2-(4-Chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (150 mg, 0.34 mmol, 1 eq) was added to EtOH (3 ml) and 2M NaOH (1.5 ml) in a reacti-vial. The vessel was heated to 100 °C. After 2 hours the reaction had gone to completion. The reaction mixture was quenched with 2M HCl solution (10 ml) and washed with EtOAc (2 x 10 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield the title compound (140 mg, 100%) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.72 (2H, s), 6.15 (1H, d, J=3.2Hz), 6.30 (1H, d, J=3.2Hz), 6.62 (1H, d, J=8.2Hz), 6.89 (1H, br t, J=7.6Hz), 7.02 (2H, d, J=8.0Hz), 7.11 (1H, dt, J=1.4, 8.0Hz), 7.11 (1H, br d, J=7.8Hz), 7.26 (4H, m), 7.78 (1H, br s), 7.93 (1H, br d, J=7.8Hz).

LC/MS t = 3.92 mins [MH^+] 418.0.

Example 20: 3-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 5-Chloro-2-(4-methoxy-benzyloxy)-benzaldehyde

5-Chloro-2-hydroxy-benzaldehyde (3.08g, 19.7mmol), 4-methoxybenzyl chloride (4ml, 29.5mmol) and potassium carbonate (5.43g, 39.3mmol) were heated in DMF at 60°C in a nitrogen atmosphere for 2 hours. Upon cooling the reaction mixture was diluted with EtOAc and washed with water. The organic layer was extracted and the aqueous layer washed with EtOAc (3 x 100ml). The combined organic extracts were then washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. This yielded the title compound as a white solid (6.64g, 100% + PMB-OH).

^{1}H-NMR (400MHz, $CDCl_3$) 3.82 (3H, s), 5.11 (2H, s), 6.93 (2H, d, J=9Hz), 7.02 (1H, d, J=9Hz), 7.35 (2H, d, J=9Hz), 7.44 (1H, dd, J=3Hz, 9Hz), 7.79 (1H, d, 3Hz), 10.4 (1H, s)

LC/MS t = 3.56 min.

b) 1-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-pentane-1,4-dione

5-Chloro-2-(4-methoxy-benzyloxy)-benzaldehyde (6.25g, 80%+PMB-OH, 18.1mmol), triethylamine (7.54ml, 54.2mmol), methyl vinyl ketone (1.53ml, 18.4mmol) and 3-ethyl-5-(2-hydroxyethyl)-4-ethylthiazolium bromide (1.37g, 5.4mmol) were refluxed in EtOH (7ml) for 18 hours. Upon cooling the reaction mixture was diluted with EtOAc and washed with saturated NH_4Cl. The organic layer was extracted and the aqueous layer washed with EtOAc (3 x 200ml). The combined organic extracts were then washed with saturated

$NaHCO_3$ and brine and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with 15% EtOAc/*iso*-hexane. This yielded the title compound as a yellow solid (4.33g, 69%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.58 (3H, s), 2.76 (2H, t, J=6Hz), 3.20 (2H, t, J=6Hz), 3.83 (3H, s), 5.08 (2H, s) 6.92 (2H, d, J=9Hz), 6.98 (1H, d, J=9Hz), 7.36 (2H, d, J=9Hz), 7.39 (1H, d, J=3Hz), 7.69 (1H, d, J=3Hz).

LC/MS t = 3.47 min

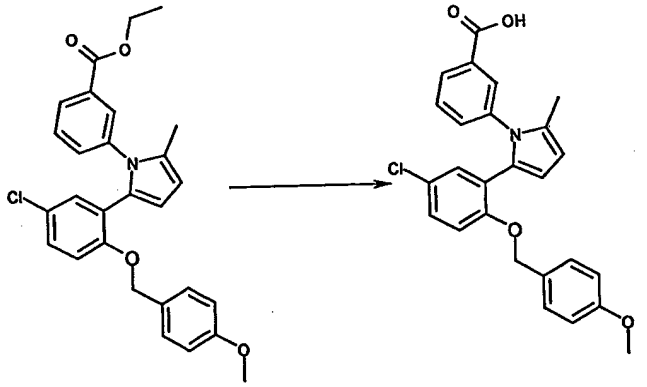
c) 3-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

1-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-pentane-1,4-dione (3g, 8.7mmol) and ethyl-3-aminobenzoate (1.55ml, 10.4mmol) were heated in toluene (1ml) in a sealed vessel at 150°C for 40 hours. Upon cooling the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel eluting with 10% EtOAc/*iso*-hexane. This yielded the title compound as a yellow oil (2.41g, 59%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.32 (3H, t, J=7Hz), 2.15 (3H, s), 3.80 (3H, s) 4.29 (2H, q, J=7Hz), 4.66 (2H, s), 6.12 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.58 (1H, d, J=9Hz), 6.81(2H, d, J=9Hz) 6.99 (2H, d, J=9Hz), 7.03 (1H, dd, J=3Hz, 9Hz), 7.09-7.12 (1H, m) 7.21 (1H, d, J=3Hz), 7.28 (1H, t, J=8Hz), 7.72 (1H, t, J=1Hz), 7.91 (1H, dt, J=1Hz, 8Hz).

LC/MS t = 4.18 [MH^+] 476 min.

d) 3-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (150 mg, 0.29 mmol, 1 eq) was added to EtOH (3 ml) and 2M NaOH (1.5 ml) in a reacti-vial. The vessel was heated to 100 °C. After 2 hours the reaction had gone to completion. The reaction mixture was quenched with 2M HCl solution (10 ml) and washed with EtOAc (2 x 10 ml). The organic extracts were combined and washed with brine (10 ml), dried over $MgSO_4$ and the solvent was then removed *in vacuo* to yield the title compound (100 mg, 71 %) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 3.78 (3H, s), 4.65 (2H, s), 6.12 (1H, d, J=3.0Hz), 6.30 (1H, d, J=3.1Hz), 6.59 (1H, d, J=8.4Hz), 6.81 (2H, d, J=8.2Hz), 7.00 (2H, d, J=8.2Hz), 7.05 (1H, dd, J=2.0, 8.2Hz), 7.15 (1H, br d, J=7.8Hz), 7.22 (1H, d, J=2.2Hz), 7.31 (1H, t, J=7.8Hz), 7.77 (1H, br s), 7.96 (1H, br d, J=8.0Hz).

LC/MS t = 3.91 mins [MH^+] 448.0.

Example 21: 3-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (2.5g, 5.2mmol) was stirred at room temperature and under nitrogen in 4.0M hydrogen chloride in dioxane (15ml) for 15 minutes. The solvent was then removed *in vacuo* and the residue diluted with EtOAc. The solution was then washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant oil was purified by chromatography on silica gel eluting with 10% EtOAc/*iso*-hexane. This yielded the title compound as a yellow oil (0.886g, 48%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.38 (3H, t, J=7Hz), 2.16 (3H, s), 4.36 (2H, q, J=7Hz), 5.87 (1H, s), 6.17(1H, d, J=3Hz), 6.36 (1H, d, J=3Hz), 6.72 (1H, d, J=3Hz), 6.80 (1H, d, 9Hz), 7.02 (1H, dd, J=3Hz, 9Hz), 7.19-7.22 (1H, m), 7.40 (1H, t, J=8Hz), 7.81 (1H, t, J=1Hz), 7.99 (1H, dt, J=1Hz, 8Hz).

LC/MS t = 3.75 min [MH^+] 356/358.

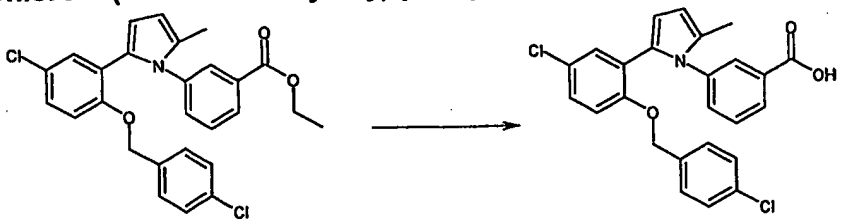
b) 3-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.148g, 0.41mmol), 4-chlorobenzyl bromide (0.128g, 0.62mmol) and potassium carbonate (0.12g, 0.82mmol) were heated in DMF at 60°C in a nitrogen atmosphere for 18 hours. Upon cooling the mixture was diluted with EtOAc and water. The organic layer was extracted and the aqueous layer washed with EtOAc. he combined organics were then washed with brine and concentrated *in vacuo*. This yielded the title compound as a clear oil (0.112g, 56%).The residue was purified by chromatography on silica gel eluting with 5% EtOAc/*iso*-hexane.

^{1}H NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7Hz), 2.15 (3H, s), 4.28 (2H, q, J=7Hz), 4.67 (2H, s), 6.14 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.52 (1H, d, J=9Hz), 6.97 (2H, d, J=9Hz), 7.05 (1H, dd, J=3Hz, 9Hz), 7.09-7.12 (1H, m), 7.22-7.30 (4H, m' excess), 7.71 (1H, t, J=1Hz), 7.91 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t = 4.34 min.

c) 3-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

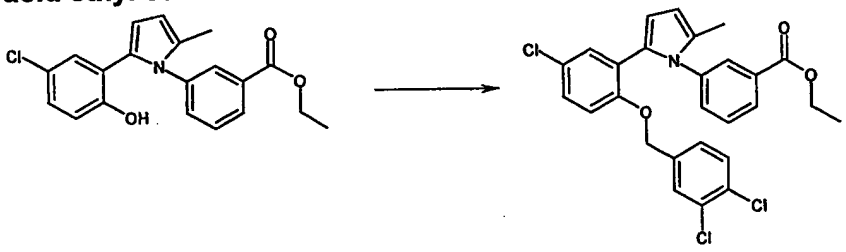


3-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.102g), 2M NaOH (1ml) and EtOH (2ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with EtOAc. The

combined organic extracts were washed with brine and dried over MgSO4, filtered and concentrated *in vacuo*, to yield a white solid (0.075g, 78%).
^{1}H-NMR (400MHz, *d*6-DMSO) 2.08 (3H, s), 4.82 (2H, s), 6.08 (1H, dd, J=0.5Hz, J=3Hz), 6.27 (1H, d, J=3Hz), 6.83 (1H, d, J=9Hz), 7.10 (1H, d, J=3Hz), 7.12 (2H, d, J=9Hz), 7.17 (1H, dd, J=3Hz, 9Hz), 7.28-7.31 (1H, m), 7.38 (2H, d, J=9Hz), 7.46 (1H, t, J=8Hz), 7.54 (1H, t, J= 0.5Hz) 7.88 (1H, dt, J=0.5Hz, 8Hz).
LC/MS t = 4.10 min [MH$^+$] 450/452/454.

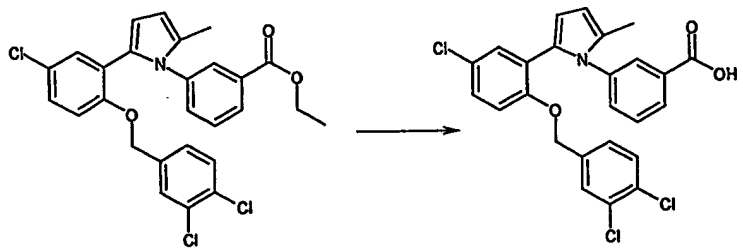
Example 22: 3-{2-[5-Chloro-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Chloro-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester



3-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.148g, 0.41mmol), 3,4-dichlorobenzyl bromide (0.107ml, 0.62mmol) and potassium carbonate (0.12g, 0.82mmol) were heated in DMF at 60°C in a nitrogen atmosphere for 18 hours. Upon cooling the mixture was diluted with EtOAc and water. The organic layer was extracted and the aqueous layer washed with EtOAc. he combined organics were then washed with brine and concentrated *in vacuo*. This yielded the title compound as a clear oil (0.151g, 70.6%).The residue was purified by chromatography on silica gel eluting with 5% EtOAc/*iso*-hexane.
^{1}H-NMR (400MHz, $CDCl_3$) 1.31 (3H, t, 7Hz), 2.17 (3H, s), 4.29 (2H, q, 7Hz), 4.67 (2H, s), 6.15 (1H, dd, J=0.5Hz, 3Hz), 6.30 (1H, d, J=3Hz), 6.50 (1H, d, J=9Hz), 6.87 (1H, dd, J=2Hz, 8Hz), 7.05 (1H, dd, J=2Hz, 9Hz), 7.10-7.15 (2H, m), 7.26 (1H, d, J=2Hz), 7.29 (1H, t, J=8Hz), 7.35 (1H, d, J=8Hz), 7.72 (1H, t, J=1Hz), 7.91 (1H, dt, J=0.5Hz, 8Hz).
LC/MS t = 4.45 min [MH$^+$] 515/517.

b) 3-{2-[5-Chloro-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Chloro-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.141g), 2M NaOH (1ml) and EtOH (2ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with EtOAc. The

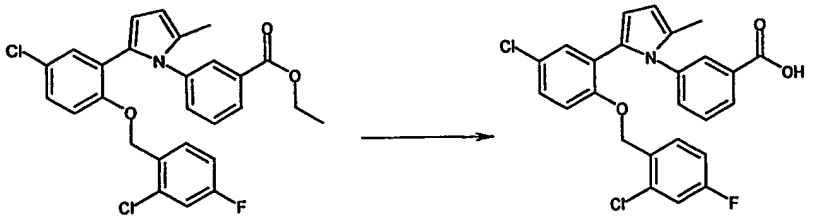
combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*, to yield a yellow oil.
^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.66 (2H, s), 6.16 (1H, dd, J=0.5Hz, J=3Hz), 6.31 (1H, d, J=3Hz), 6.52 (1H, d, J=9Hz), 6.89 (1H, dd, J=2Hz, 8Hz), 7.08 (1H, dd, J=2Hz, 9Hz), 7.14 (1H, d, J=2Hz), 7.15-7.19 (1H, m), 7.27 (1H, m' excess), 7.33 (1H, t, J=8Hz), 7.35 (1H, d, J=8Hz), 7.77 (1H, t, J=0.5Hz), 7.98 (1H, dt, J=0.5Hz, 8Hz).
LC/MS t = 4.25 min [MH^+] 487/489.

Example 23: 3-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.148g, 0.41mmol), 2-chloro-4-fluoro-benzyl bromide (0.139g, 0.62mmol) and potassium carbonate (0.12g, 0.82mmol) were heated in DMF at 60°C in a nitrogen atmosphere for 18 hours. Upon cooling the mixture was diluted with EtOAc and water. The organic layer was extracted and the aqueous layer washed with EtOAc. The combined organics were then washed with brine and concentrated *in vacuo*. This yielded the title compound as a clear oil (0.149g, 72%).The residue was purified by chromatography on silica gel eluting with 5% EtOAc/*iso*-hexane.
^{1}H-NMR (400MHz, $CDCl_3$) 1.31 (3H, t, 7Hz), 2.17 (3H, s), 4.29 (2H, q, 7Hz), 4.73 (2H, s), 6.13 (1H, dd, J=0.5Hz, 3Hz), 6.31 (1H, d, 3Hz), 6.52 (1H, d, 9Hz), 6.85-6.91 (2H, m), 7.05-7.10 (2H, m), 7.15 (1H, m), 7.25 (1H, d, J=3Hz), 7.30 (1H, t, J=8Hz), 7.74 (1H, t, J=0.5Hz), 7.92 (1H, dt, J=0.5Hz, 8Hz).
LC/MS t = 4.36 min [MH^+] 498/500/502.

b) 3-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.139g), 2M NaOH (1ml) and EtOH (2ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*, to yield a yellow oil.
^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.75 (2H, s), 6.16 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.56 (1H, d, J=9Hz), 6.87-6.97 (2H, m), 7.03-7.10 (2H, m), 7.17-7.21 (1H, m), 7.24 (1H, d, J=3Hz), 7.34 (1H, t, J=8Hz), 7.79 (1H, t, J=0.5Hz), 7.99 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t = 4.13 min [MH^+] 470/472/474.

Example 24: 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

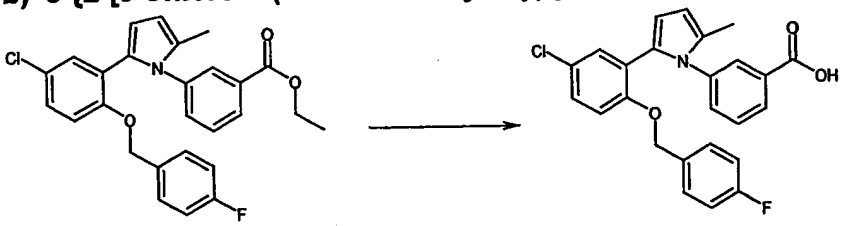
a) 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.148g, 0.41mmol), 4-fluorobenzyl bromide (0.078ml, 0.62mmol) and potassium carbonate (0.12g, 0.82mmol) were heated in DMF at 60°C in a nitrogen atmosphere for 18 hours. Upon cooling the mixture was diluted with EtOAc and water. The organic layer was extracted and the aqueous layer washed with EtOAc. The combined organics were then washed with brine and concentrated *in vacuo*. This yielded the title compound as a clear oil (0.142g, 74%).The residue was purified by chromatography on silica gel eluting with 5% EtOAc/*iso*-hexane.

^{1}H-NMR (400MHz, $CDCl_3$) 1.31 (3H, t, 7Hz), 2.16 (3H, s), 4.29 (2H, q, 7Hz), 4.68 (2H, s), 6.13 (1H, d, J=3Hz), 6.30 (1H, d, 3Hz), 6.54 (1H, d, 9Hz), 6.96-7.06 (5H, m), 7.10 (1H, dt, J=0.5Hz, J=8Hz), 7.23 (1H, d, J=3Hz), 7.28 (1H, t, J=8Hz), 7.70 (1H, t, J=0.5Hz), 7.90 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t = 4.22 min [MH^+] 464/466.

b) 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.132g), 2M NaOH (1ml) and EtOH (2ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*, to yield a yellow solid (0.105g, 85%).

^{1}H-NMR (400MHz, DMSO) 2.08 (3H, s), 4.80 (2H, s), 6.07 (1H, dd, J=0.5Hz, 3Hz), 6.24 (1H, d, J=3Hz), 6.89 (1H, d, J=9Hz), 7.09 (1H, d, J=3Hz), 7.10-7.20 (5H, m), 7.25-7.29 (1H, m), 7.45 (1H, t, J=8Hz), 7.52 (1H, t, J=0.5Hz), 7.87 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t = 3.96 min [MH^+] 436/438.

Example 25: 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

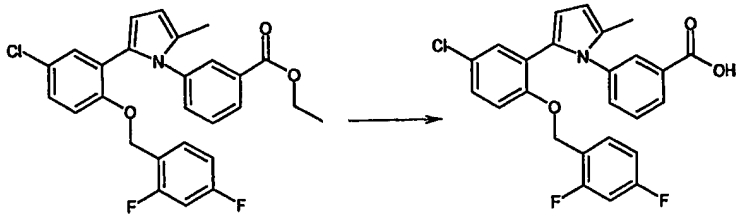
3-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.148g, 0.41mmol), 2,4-difluorobenzyl bromide (0.078ml, 0.62mmol) and potassium carbonate

(0.12g, 0.82mmol) were heated in DMF at 60°C in a nitrogen atmosphere for 18 hours. Upon cooling the mixture was diluted with EtOAc and water. The organic layer was extracted and the aqueous layer washed with EtOAc. The combined organics were then washed with brine and concentrated *in vacuo*. This yielded the title compound as a clear oil (0.143g, 71%).The residue was purified by chromatography on silica gel eluting with 5% EtOAc/*iso*-hexane.

^{1}H-NMR (400MHz, $CDCl_3$) 1.31 (3H, t, 7Hz), 2.16 (3H, s), 4.30 (2H, q, 7Hz), 4.73 (2H, s), 6.13 (1H, dd, J=0.5Hz, J=3Hz), 6.30 (1H, d, 3Hz), 6.59 (1H, d, 9Hz), 6.76-6.81 (2H, m), 6.93-6.99 (1H, m,), 7.07 (1H, dd, J=1.5Hz, 9Hz) 7.13 (1H, m), 7.21 (1H, d, J=3Hz), 7.29 (1H, t, J=8Hz), 7.72 (1H, t, J=1Hz), 7.91 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t = 4.24 min [MH^+] 482/484.

b) 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.133g), 2M NaOH (1ml) and EtOH (2ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*, to yield a yellow solid (0.103g, 82%).

^{1}H-NMR (400MHz, *d*6-DMSO) 2.08 (3H, s), 4.84 (2H, s), 6.07 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.97 (1H, d, J=9Hz), 7.07 (1H, ddd, J=2Hz, 9Hz), 7.09 (1H, d, J=3Hz), 7.18-7.30 (4H, m), 7.46 (1H, t, J=8Hz), 7.52 (1H, t, J=0.5Hz), 7.87 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t = 3.98 min [MH^+] 454/456.

<u>Example 26: 5-{2-[2-(4-Methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid</u>

a) 5-Amino-nicotinic acid

Copper (II) sulfate (12.5g, 50mmol) was added to 5-bromo-nicotinic acid (50g, 248mmol) in aqueous ammonium hydroxide solution (d = 0.88). The reaction was sealed in an autoclave reactor and heated at 180°C for 15 hours. The mixture was cooled, diluted with water (300ml), sodium sulfite (13.5g, 173mmol) was added and the mixture stirred for 20 minutes. The black precipitate was filtered away through celite, and the filtrate was adjusted to pH 3-4 upon treatment with 2M HCl. The mixture was filtered through celite and the filtrate concentrated to 200ml volume upon which a white precipitate formed. The solution was cooled, filtered and the solid dried under vacuum at 40°C overnight to give the title compound (22g, 159mmol, 64%).

^{1}NMR (400MHz, *d*6-DMSO) 5.60 (2H, broad s), 7.41 (1H, d, J=3Hz), 8.10 (1H, d, J=3Hz), 8.24 (1H, d, J=3Hz), 13.05 (1H, broad s).
GC/MS [MH+] 139.

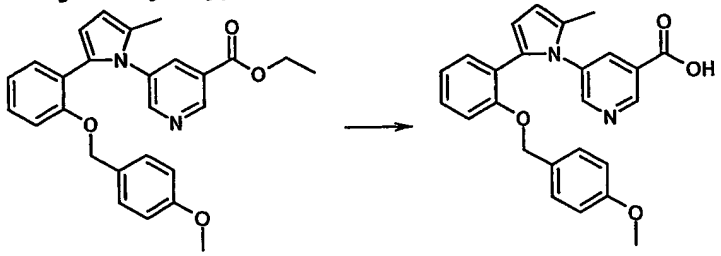
b) 5-Amino-nicotinic acid ethyl ester

HCl (4M in dioxane, 100ml, 0.4mol) was added to 5-Amino-nicotinic acid (22g, 159mmol) in ethanol (500ml) and heated at reflux for 16 hours. The reaction was cooled, concentrated and partitioned between ethyl acetate and saturated $NaHCO_3$. The aqueous was extracted with EtOAc and the combined organics washed with brine, dried ($MgSO_4$), filtered and concentrated to give the title compound (22g, 159mmol, 83%).
^{1}H NMR (400MHz, $CDCl_3$) 1.40 (3H, t, J=7Hz), 3.83 (2H, broad s), 4.39 (2H, q, J=7Hz), 7.57 (1H, dd, J=2, 3Hz), 8.23 (1H, d, J=3Hz), 8.63 (1H, d, J=2Hz).
LC/MS t=1.48 min [MH+] 167.

c) 5-{2-[2-(4-Methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

1-[2-(4-Methoxy-benzyloxy)-phenyl]-pentane-1,4-dione (1.05g, 3.3mmol) and 5-amino-nicotinic acid ethyl ester (0.6g, 3.7mmol) were heated in toluene (1ml) in a sealed vessel at 150°C for 3 days. Upon cooling, the mixture was diluted with EtOAc and washed with 2M HCl and saturated $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with *iso*hexane / EtOAc (10%) as eluant, to give the title compound (530mg, 36%).
^{1}H NMR (400MHz, $CDCl_3$) 1.33 (3H, t, J=7.5Hz), 2.16 (3H, s), 3.81 (3H, s), 4.32 (2H, q, J=7.5Hz), 4.67 (2H, s), 6.16 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.69 (1H, broad d, J=8.5Hz), 6.83 (2H, d, J=9Hz), 6.91 (1H, ddd, J=1, 7Hz), 7.02 (2H, d, J=9Hz), 7.15 (1H, ddd, J=2, 7Hz), 7.29 (1H, dd, J=2, 8.5Hz), 7.88 (1H, t, J=2Hz), 8.35 (1H, d, J=2Hz), 9.01 (1H, d, J=2Hz).
LC/MS t=3.80 min [MH+] 443.

d) 5-{2-[2-(4-Methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[2-(4-Methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (70mg, 0.16mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (3ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (57mg, 87%).
^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 3.76 (3H, s), 4.65 (2H, s), 6.18 (1H, dd, J=1, 3.5Hz), 6.30 (1H, d, J=3.5Hz), 6.71 (1H, broad d, J=8.5Hz), 6.82 (2H, d, J=9Hz), 6.93 (1H, ddd, J=1, 8Hz), 7.02 (2H, d, J=9Hz), 7.16 (1H, ddd, J=2, 8Hz), 7.31 (1H, dd, J=2, 8Hz), 7.92 (1H, t, J=2Hz), 8.38 (1H, d, J=2Hz), 9.08 (1H, d, J=2Hz).

LC/MS t=3.63 min [MH-] 413.

Example 27: 5-{2-[2-(4-Chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

a) 5-{2-[2-(Hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

HCl (4M in dioxane, 2.5ml, 10mmol) was added to 5-{2-[2-(4-Methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (460mg, 1mmol) and stirred at room temperature for 1 hour. The reaction was concentrated and the residue partitioned between CH_2Cl_2 and $NaHCO_3$. The organics were washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography, with *iso*hexane / EtOAc (30%) as eluant, to give the title compound (200mg, 67%).

^{1}H NMR (400MHz, $CDCl_3$) 1.38 (3H, t, J=7Hz), 2.18 (3H, s), 4.39 (2H, q, J=7Hz), 6.21 (1H, broad d, J=3Hz), 6.39 (1H, d, J=3Hz), 6.67 (1H, ddd, J=1, 8Hz), 6.74 (1H, dd, J=2, 8Hz), 7.10 (1H, ddd, J=2, 8Hz), 7.38 (1H, dd, J=3, 8.5Hz), 8.04 (1H, t, J=2Hz), 8.48 (1H, d, J=2Hz), 9.09 (1H, d, J=2Hz).

LC/MS t=3.25 min [MH+] 323.

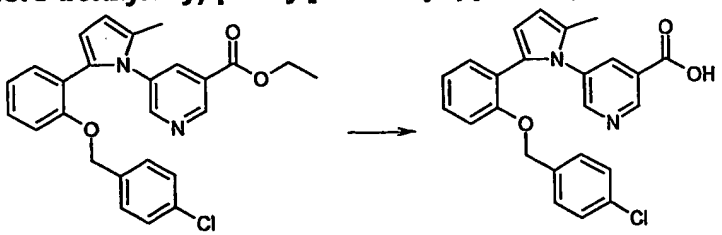
b) 5-{2-[2-(4-Chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

4-Chloro-benzyl bromide (48mg, 0.23mmol) was added to 5-{2-[2-(Hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (50mg, 0.16mmol) and K_2CO_3 (43mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with *iso*hexane / EtOAc (10%) as eluant, to give the title compound (15mg, 21%).

^{1}H NMR (400MHz, $CDCl_3$) F4743 1.33 (3H, t, J=7Hz), 2.17 (3H, s), 4.32 (2H, q, J=7Hz), 4.70 (2H, s), 6.17 (1H, dd, J=1, 3Hz), 6.30 (1H, d, J=3Hz), 6.64 (1H, broad d, J=8Hz), 6.93 (1H, ddd, J=1, 8Hz), 7.01 (2H, d, J=1Hz), 7.15 (1H, ddd, J=2, 8Hz), 7.16 (1H, ddd, J=2, 8Hz), 7.27 (2H, d, J=8Hz), 7.30 (1H, dd, J=2, 8Hz), 7.89 (1H, t, J=2Hz), 8.35 (1H, d, 2Hz), 9.02 (1H, broad s).

LC/MS t=3.98 min [MH+] 447/449.

c) 5-{2-[2-(4-Chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[2-(4-Chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (15mg, 0.03mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (10mg, 71%).

^{1}H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.69 (2H, s), 6.18 (1H, broad d, J=3.5Hz), 6.31 (1H, d, J=3.5Hz), 6.65 (1H, broad d, J=8Hz), 6.94 (1H, broad t, J=8Hz), 7.12 (2H, d,

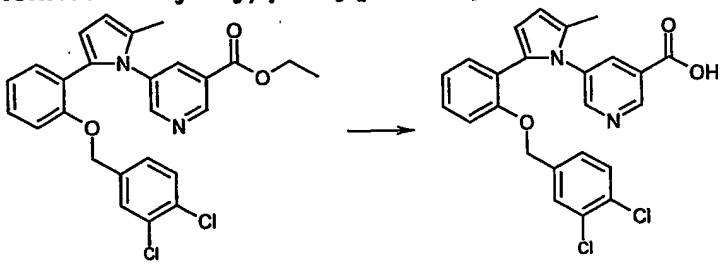
J=8Hz), 7.16 (1H, ddd, J=2, 8Hz), 7.28 (2H, d, J=8Hz), 7.31 (1H, dd, J=2, 8Hz), 7.90 (1H, t, J=2Hz), 8.39 (1H, broad s), 9.06 (1H, broad s).
LC/MS t=3.85 min [MH+] 419/421.

Example 28: 5-{2-[2-(3,4-Dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

a) 5-{2-[2-(3,4-Dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

3,4-Dichloro-benzyl bromide (0.04ml, 0.23mmol) was added to 5-{2-[2-(Hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (50mg, 0.16mmol) and K_2CO_3 (43mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with *iso*hexane / EtOAc (10%) as eluant, to give the title compound (13mg, 17%).
^{1}H NMR (400MHz, $CDCl_3$) 1.32 (3H, t, J=7Hz), 2.18 (3H, s), 4.31 (2H, q, J=7Hz), 4.68 (2H, s), 6.19 (1H, dd, J=1, 3Hz), 6.30 (1H, d, J=3Hz), 6.62 (1H, dd, J=8Hz), 6.87-6.98 (2H, m), 7.12-7.22 (2H, m), 7.28-7.38 (2H, m), 7.91 (1H, t, J=2Hz), 8.38 (1H, d, 2Hz), 9.02 (1H, broad s).
LC/MS t=4.10 min [MH+] 481/483/485.

b) 5-{2-[2-(3,4-Dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[2-(3,4-Dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (13mg, 0.03mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (10mg, 82%).
^{1}H NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 4.68 (2H, s), 6.19 (1H, dd, J=1, 3Hz), 6.20 (1H, d, J=3Hz), 6.32 (1H, dd, J=4Hz), 6.64 (1H, d, J=8Hz), 6.90-7.00 (2H, m), 7.13-7.20 (2H, m), 7.33 (1H, dd, J=2, 8Hz), 7.37 (1H, d, J=8Hz), 7.92 (1H, t, J=2Hz), 8.42 (1H, d, 2Hz), 9.07 (1H, d, J=2Hz).
LC/MS t=4.06 min [MH+] 453/455/457.

Example 29: 5-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

a) 5-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

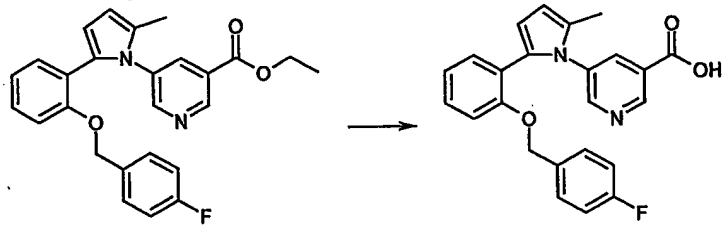
4-Fluoro-benzyl bromide (0.029ml, 0.23mmol) was added to 5-{2-[2-(Hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (50mg, 0.16mmol) and K_2CO_3 (43mg,

0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried (MgSO4), filtered and concentrated. The residue was purified by chromatography on silica gel with *iso*hexane / EtOAc (10%) as eluant, to give the title compound (20mg, 30%).

^{1}H NMR (400MHz, $CDCl_3$) 1.33 (3H, t, J=7Hz), 2.16 (3H, s), 4.31 (2H, q, J=7Hz), 4.69 (2H, s), 6.17 (1H, broad d, J=3.5Hz), 6.30 (1H, d, J=3.5Hz), 6.67 (1H, broad d, J=8Hz), 6.90-7.08 (5H, m), 7.15 (1H, ddd, J=2, 8Hz), 7.29 (1H, dd, J=2, 8Hz), 7.87 (1H, t, J=2Hz), 8.34 (1H, d, 2Hz), 9.01 (1H, d, J=2Hz).

LC/MS t=3.84 min [MH+] 431

b) 5-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (16mg, 0.04mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (13mg, 87%).

^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.68 (2H, s), 6.18 (1H, broad d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.68 (1H, broad d, J=8Hz), 6.92-7.02 (3H, m), 7.03-7.10 (2H, m), 7.17 (1H, ddd, J=2, 8Hz), 7.32 (1H, dd, J=2, 8Hz), 7.90 (1H, broad s), 8.38 (1H, broad s), 9.07 (1H, broad s).

LC/MS t=3.65 min [MH+] 403.

Example 30: 5-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

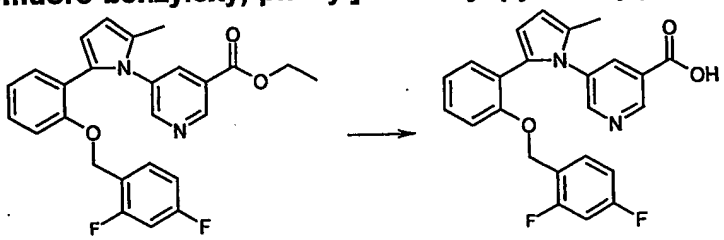
a) 5-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

2,4-Difluoro-benzyl bromide (0.030ml, 0.23mmol) was added to 5-{2-[2-(Hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (50mg, 0.16mmol) and K_2CO_3 (43mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with *iso*hexane / EtOAc (10%) as eluant, to give the title compound (19mg, 27%).

^{1}H NMR (400MHz, $CDCl_3$) 1.34 (3H, t, J=7Hz), 2.17 (3H, s), 4.33 (2H, q, J=7Hz), 4.76 (2H, s), 6.17 (1H, dd, J=1, 3.5Hz), 6.29 (1H, d, J=3.5Hz), 6.70 (1H, broad d, J=8Hz), 6.74-6.84 (2H, m), 6.93 (1H, ddd, J=1, 8Hz), 6.97-7.06(1H, m), 7.17 (1H, ddd, J=2,8Hz), 7.27 (1H, dd, J=2, 8Hz), 7.91 (1H, t, J=2Hz), 8.37 (1H, broad d, 2Hz), 9.03 (1H, broad s).

LC/MS t=3.86 min [MH+] 449.

b) 5-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (13mg, 0.03mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (10mg, 82%).

^{1}H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.75 (2H, s), 6.18 (1H, broad d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.68-6.85 (3H, m), 6.92-7.09 (3H, m), 7.19 (1H, broad ddd, J=8Hz), 7.30 (1H, dd, J=2, 8Hz), 7.96 (1H, broad s), 8.42 (1H, broad s), 9.10 (1H, broad s).

LC/MS t=3.66 min [MH+] 421.

Example 31: 5-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

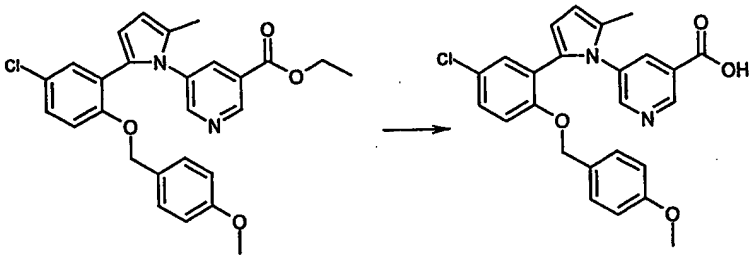
a) 5-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

1-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-pentane-1,4-dione (1.04g, 3.0mmol) and 5-amino-nicotinic acid ethyl ester (0.55g, 3.3mmol) were heated in toluene (0.5ml) in a sealed vessel at 150°C for 3 days. Upon cooling, the mixture was diluted with EtOAc and washed with 2M HCl and saturated $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with *iso*hexane containing a gradient of EtOAc (15-20%) as eluant, to give the title compound (740mg, 52%).

^{1}H NMR (400MHz, $CDCl_3$) 1.34 (3H, t, J=7.5Hz), 2.15 (3H, s), 3.80 (3H, s), 4.33 (2H, q, J=7.5Hz), 4.61 (2H, s), 6.16 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.60 (1H, broad d, J=9Hz), 6.83 (2H, d, J=9Hz), 6.97 (2H, d, J=9Hz), 7.09 (1H, dd, J=2.5, 9Hz), 7.29 (1H, d, J=2.5Hz), 7.87 (1H, t, J=2Hz), 8.35 (1H, d, J=2Hz), 9.04 (1H, d, J=2Hz).

LC/MS t=3.96 min [MH+] 477/479.

b) 5-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (90mg, 0.16mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate,

washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (75mg, 89%).

^1H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 3.79 (3H, s), 4.61 (2H, s), 6.17 (1H, dd, J=1, 4Hz), 6.30 (1H, d, J=4Hz), 6.62 (1H, d, J=9Hz), 6.83 (2H, d, J=9Hz), 6.98 (2H, d, J=9Hz), 7.10 (1H, dd, J=3, 9Hz), 7.31 (1H, d, J=3Hz), 7.89 (1H, t, J=2Hz), 8.37 (1H, d, J=2Hz), 9.08 (1H, d, J=2Hz).

LC/MS t=3.81 min [MH-] 447/449.

Example 32: 5-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

a) 5-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

HCl (4M in dioxane, 2.5ml, 10mmol) was added to 5-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (640mg, 1.3mmol) and stirred at room temperature for 30 minutes. The reaction was concentrated and the residue partitioned between EtOAc and $NaHCO_3$. The organics were washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with *iso*hexane / EtOAc (20%) as eluant, to give the title compound (320mg, 67%).

^1H NMR (400MHz, $CDCl_3$) 1.39 (3H, t, J=7Hz), 2.17 (3H, s), 4.39 (2H, q, J=7Hz), 6.20 (1H, d, J=3.5Hz), 6.37 (1H, d, J=3.5Hz), 6.74 (1H, d, J=9Hz), 6.87 (1H, d, J=2.5Hz), 7.05 (1H, dd, J=2.5, 9Hz), 8.04 (1H, t, J=2Hz), 8.49 (1H, d, J=2Hz), 9.06 (1H, d, J=2Hz).

LC/MS t=3.48 min [MH+] 357/359.

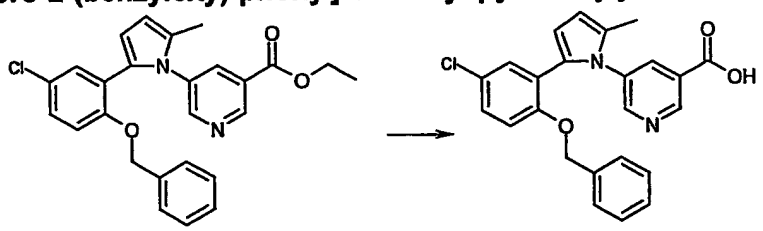
b) 5-[2-(5-Chloro-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-nicotinic acid ethyl ester

Benzyl bromide (0.025ml, 0.21mmol) was added to 5-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (50mg, 0.14mmol) and K_2CO_3 (43mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with *iso*hexane / EtOAc (15%) as eluant, to give the title compound (35mg, 56%).

^1H NMR (400MHz, $CDCl_3$) 1.34 (3H, t, J=7Hz), 2.15 (3H, s), 4.34 (2H, q, J=7Hz), 4.70 (2H, s), 6.17 (1H, d, J=3.5Hz), 6.31 (1H, d, J=3.5Hz), 6.58 (1H, d, J=9Hz), 7.00-7.05 (2H, m), 7.09 (1H, dd, J=3, 9Hz), 7.26-7.32 (4H, m), 7.90 (1H, t, J=2Hz), 8.36 (1H, d, 2Hz), 9.04 (1H, d, J=2Hz).

LC/MS t=3.98 min [MH+] 447/449.

c) 5-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (35mg, 0.08mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed

with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (24mg, 73%).

^{1}H NMR (400MHz, *d*6-DMSO) 2.10 (3H, s), 4.78 (2H, s), 6.13 (1H, dd, J=1, 3.5Hz), 6.28 (1H, d, J=3.5Hz), 6.84 (1H, d, J=9Hz), 7.05-7.11 (2H, m), 7.20-7.34 (5H, m), 7.83 (1H, t, J=2Hz), 8.43 (1H, d, J=2Hz), 8.95 (1H, d, J=2Hz), 13.48 (1H, broad s).

LC/MS t=3.86 min [MH+] 419/421.

Example 33: 5-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

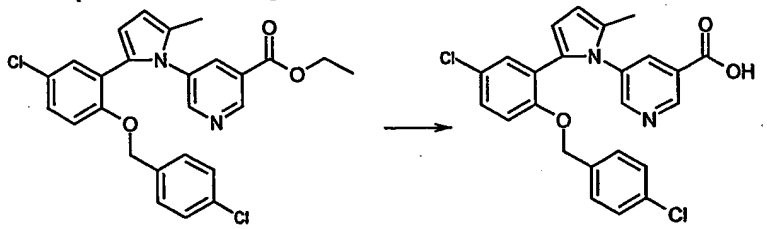
a) 5-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

4-Chloro-benzyl bromide (43mg, 0.21mmol) was added to 5-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (50mg, 0.14mmol) and K_2CO_3 (43mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with *iso*hexane / EtOAc (15%) as eluant, to give the title compound (30mg, 44%).

^{1}H NMR (400MHz, $CDCl_3$) 1.35 (3H, t, J=7Hz), 2.16 (3H, s), 4.33 (2H, q, J=7Hz), 4.65 (2H, s), 6.17 (1H, dd, J=1, 3.5Hz), 6.30 (1H, d, J=3.5Hz), 6.55 (1H, d, J=9Hz), 6.97 (2H, d, J=8.5Hz), 7.10 (1H, dd, J=2.5, 9Hz), 7.27 (2H, d, J=8.5Hz), 7.31 (1H, d, J=2.5Hz), 7.88 (1H, t, J=2Hz), 8.36 (1H, d, 2Hz), 9.04 (1H, d, J=2Hz).

LC/MS t=4.12 min [MH+] 481/483/485.

b) 5-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (30mg, 0.06mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (22mg, 78%).

^{1}H NMR (400MHz, *d*6-DMSO) 2.10 (3H, s), 4.77 (2H, s), 6.13 (1H, dd, J=1, 3.5Hz), 6.28 (1H, d, J=3.5Hz), 6.83 (1H, d, J=9Hz), 7.10 (2H, d, J=8.5Hz), 7.21-7.27 (2H, m), 7.37 (2H, d, J=8.5Hz), 7.82 (1H, t, J=2Hz), 8.43 (1H, d, J=2Hz), 8.92 (1H, d, J=2Hz), 13.43 (1H, broad s).

LC/MS t=4.08 min [MH+] 453/455/457.

Example 34: 5-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

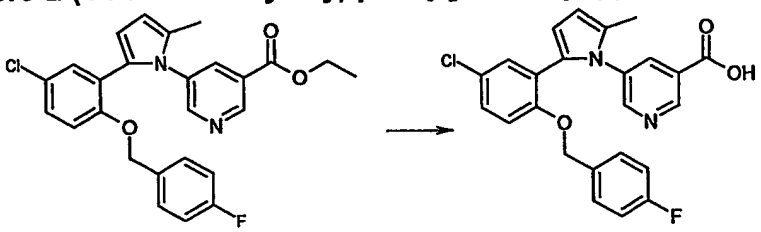
a) 5-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

4-Fluoro-benzyl bromide (0.027ml, 0.21mmol) was added to 5-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (50mg, 0.14mmol) and K_2CO_3 (43mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with *iso*hexane / EtOAc (15%) as eluant, to give the title compound (35mg, 54%).

^{1}H NMR (400MHz, $CDCl_3$) 1.35 (3H, t, J=7Hz), 2.15 (3H, s), 4.33 (2H, q, J=7Hz), 4.64 (2H, s), 6.17 (1H, dd, J=1, 3.5Hz), 6.30 (1H, d, J=3.5Hz), 6.58 (1H, d, J=9Hz), 6.96-7.05 (4H, m), 7.10 (1H, ddd, J=3, 9Hz), 7.31 (1H, d, J=2.5Hz), 7.86 (1H, t, J=2Hz), 8.34 (1H, d, 2Hz), 9.04 (1H, d, J=2Hz).

LC/MS t=3.99 min [MH+] 465/467.

b) 5-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (35mg, 0.08mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (25mg, 76%).

^{1}H NMR (400MHz, *d*6-DMSO) 2.08 (3H, s), 4.77 (2H, s), 6.11 (1H, broad d, J=3.5Hz), 6.26 (1H, d, J=3.5Hz), 6.87 (1H, d, J=9Hz), 7.11-7.25 (6H, m), 7.81 (1H, broad s), 8.34 (1H, d, J=2Hz), 8.92 (1H, d, J=2Hz).

LC/MS t=3.87 min [MH+] 437/439.

Example 35: 5-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

a) 5-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

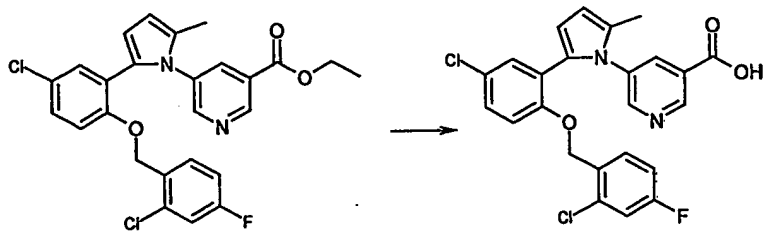
2-Chloro-4-fluoro-benzyl bromide (47mg, 0.21mmol) was added to 5-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (50mg, 0.14mmol) and K_2CO_3 (43mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with *iso*hexane / EtOAc (15%) as eluant, to give the title compound (39mg, 56%).

^{1}H NMR (400MHz, $CDCl_3$) 1.35 (3H, t, J=7Hz), 2.17 (3H, s), 4.34 (2H, q, J=7Hz), 4.73 (2H, s), 6.17 (1H, dd, J=1, 3.5Hz), 6.32 (1H, d, J=3.5Hz), 6.57 (1H, d, J=9Hz), 6.88-6.94

(2H, m), 7.07-7.14 (2H, m), 7.30 (1H, d, J=3Hz), 7.92 (1H, t, J=2Hz), 8.40 (1H, d, 2Hz), 9.06 (1H, d, J=2Hz).

LC/MS t=4.14 min [MH+] 499/501/503.

b) 5-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (39mg, 0.08mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (28mg, 76%).

^{1}H NMR (400MHz, *d*6-DMSO) 2.10 (3H, s), 4.78 (2H, s), 6.13 (1H, dd, J=1, 3.5Hz), 6.29 (1H, d, J=3.5Hz), 6.93 (1H, d, J=9Hz), 7.07-7.14 (1H, m), 7.19 (1H, ddd, J=2.5, 9Hz), 7.23-7.29 (2H, m), 7.46 (1H, dd, J=2.5, 9Hz), 7.78 (1H, t, J=2Hz), 8.40 (1H, d, J=2Hz), 8.94 (1H, d, J=2Hz), 13.47 (1H, broad s).

LC/MS t=4.08 min [MH-] 469/471/473.

Example 36: 5-{2-[5-Chloro-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

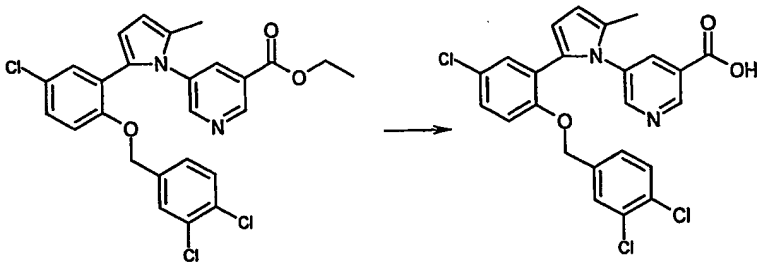
a) 5-{2-[5-Chloro-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

3,4-Dichloro-benzyl bromide (0.036ml, 0.21mmol) was added to 5-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (50mg, 0.14mmol) and K_2CO_3 (43mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried (MgSO4), filtered and concentrated. The residue was purified by chromatography on silica gel with *iso*hexane / EtOAc (15%) as eluant, to give the title compound (31mg, 43%).

^{1}H NMR (400MHz, $CDCl_3$) 1.34 (3H, t, J=7Hz), 2.18 (3H, s), 4.33 (2H, q, J=7Hz), 4.64 (2H, s), 6.18 (1H, dd, J=1, 3.5Hz), 6.31 (1H, d, J=3.5Hz), 6.54 (1H, d, J=9Hz), 6.88 (1H, dd, J=2, 8Hz), 7.09-7.13 (2H, m), 7.32 (1H, d, J=3Hz), 7.38 (1H, d, J=8.5Hz), 7.90 (1H, t, J=2Hz), 8.39 (1H, d, 2Hz), 9.05 (1H, d, J=2Hz).

LC/MS t=4.23 min [MH+] 515/517/519.

b) 5-{2-[5-Chloro-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[5-Chloro-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (31mg, 0.06mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (23mg, 79%).

^{1}H NMR (400MHz, *d*6-DMSO) 2.13 (3H, s), 4.80 (2H, s), 6.16 (1H, dd, J=1, 3.5Hz), 6.30 (1H, d, J=3.5Hz), 6.83 (1H, d, J=9Hz), 7.05 (1H, dd, J=2, 8.5Hz), 7.23-7.31 (3H, m), 7.58 (1H, d, J=8.5Hz), 7.84 (1H, t, J=2Hz), 8.44 (1H, d, J=2Hz), 8.94 (1H, d, J=2Hz), 13.50 (1H, broad s).

LC/MS t=4.26 min [MH+] 487/489/491.

Example 37: 5-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

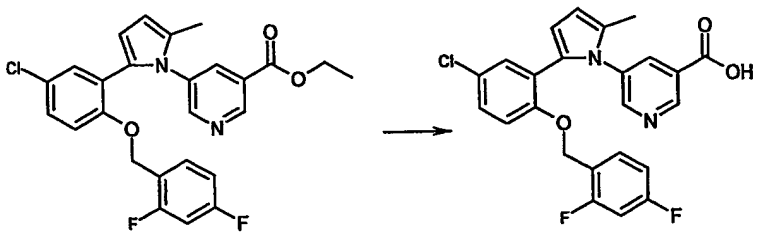
a) 5-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

2,4-Difluoro-benzyl bromide (0.027ml, 0.21mmol) was added to 5-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (50mg, 0.14mmol) and K_2CO_3 (43mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried (MgSO4), filtered and concentrated. The residue was purified by chromatography on silica gel with *iso*hexane / EtOAc (15%) as eluant, to give the title compound (40mg, 59%).

^{1}H NMR (400MHz, $CDCl_3$) 1.36 (3H, t, J=7Hz), 2.16 (3H, s), 4.35 (2H, q, J=7Hz), 4.71 (2H, s), 6.16 (1H, dd, J=1, 3.5Hz), 6.29 (1H, d, J=3.5Hz), 6.62 (1H, d, J=9Hz), 6.75-6.84 (2H, m), 6.97 (1H, ddd, J=2, 7Hz), 7.12 (1H, dd, J=2, 9Hz), 7.28 (2H, d, J=2Hz), 7.90 (1H, t, J=2Hz), 8.37 (1H, d, 2Hz), 9.05 (1H, d, J=2Hz).

LC/MS t=4.00 min [MH+] 482/484.

b) 5-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (40mg, 0.08mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in

a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (30mg, 80%).

^{1}H NMR (400MHz, *d*6-DMSO) 2.08 (3H, s), 4.77 (2H, s), 6.12 (1H, broad d, J=3.5Hz), 6.26 (1H, d, J=3.5Hz), 6.97 (1H, d, J=9Hz), 7.05 (1H, ddd, J=2.5, 9Hz), 7.11-7.29 (4H, m), 7.76 (1H, t, J=2Hz), 8.36 (1H, d, J=2Hz), 8.93 (1H, d, J=2Hz), 13.47 (1H, broad s).

LC/MS t=3.88 min [MH-] 453/455.

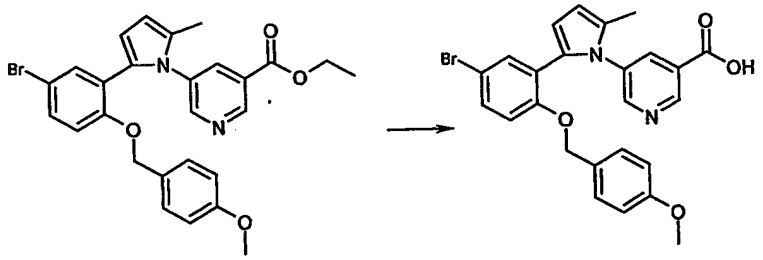
Example 38: 5-{2-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

a) 5-{2-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

1-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-pentane-1,4-dione (134mg, 0.34mmol) and 5-amino-nicotinic acid ethyl ester (62mg, 0.37mmol) were heated in toluene (0.5ml) in a sealed vessel at 150°C for 3 days. Upon cooling, the mixture was diluted with EtOAc and washed with 2M HCl and saturated $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography, using Biotage□, with *iso*hexane containing a gradient of EtOAc (15-20%) as eluant, to give the title compound (60mg, 36%).

LC/MS t=3.99 min [MH+] 521/523

b) 5-{2-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (10mg, 0.02mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (7mg, 74%).

^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 3.76 (3H, s), 4.60 (2H, s), 6.16 (1H, d, J=3.5Hz), 6.30 (1H, d, J=3.5Hz), 6.56 (1H, d, J=9Hz), 6.82 (2H, d, J=9Hz), 6.98 (2H, d, J=9Hz), 7.23 (1H, dd, J=2.5, 9Hz), 7.46 (1H, d, J=2.5Hz), 7.91 (1H, t, J=2Hz), 8.36 (1H, d, J=2Hz), 9.09 (1H, d, J=2Hz).

LC/MS t=9.83 min [MH+] 493/49.

Example 39: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chlorobenzoic acid

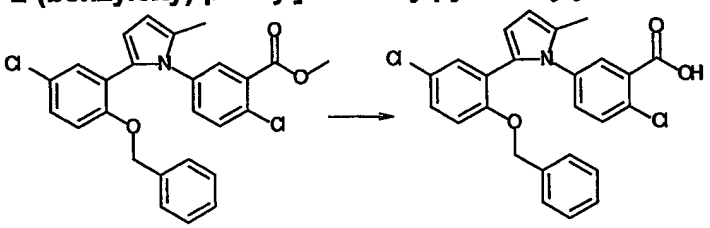
a) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester

1-[5-Chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione (160mg, 0.5mmol) was treated with 5-amino-2-chloro-benzoic acid methyl ester (100mg, 0.55mol) (Brown *et al*, WO0055120), and p-toluenesulfonic acid (~30mg) in toluene (4ml). The reaction mixture was then refluxed over 18hrs under nitrogen, evaporated down to an oil, dissolved in as little DCM as possible, and placed on a Water's silica cartridge (10g) saturated with iso-hexane. The column was then eluted with iso-hexane (~50ml) followed by an Et_2O/iso-hexane gradient mixture starting at 10% Et_2O to give the title compound (34mg, 7%).

^{1}H NMR (400MHz, $CDCl_3$) 2.23 (3H, s), 3.8 (3H, s), 4.72 (2H, s), 6.12 (1H, d, J-3Hz), 6.28 (1H, d, J=3Hz), 6.58 (1H, d, J=9Hz), 6.94 (1H, dd, J=2, 8Hz), 7.69-7.05 (2H, m), 7.08 (1H, dd, J=2.8Hz), 7.22 (5H, m), 7.48 (1H, d, J=2Hz).

LC/MS t=4.14 min, [MH+] 466/468/470.

b) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chlorobenzoic acid



3-[2-(5-Chloro-2-benzyloxy-phenyl)-5-methylpyrrol-1-yl]-6-chlorobenzoic acid methylester (34mg) was treated with 2M NaOH (3ml) in MeOH (4ml) and heated at reflux for 2 hrs under nitrogen. The reaction mixture was then reduced *in vacuo*, diluted with water (~10ml), treated with 2M HCl (~3ml), then adjusted to pH~4 with a few drops of glacial acetic acid. The aqueous was extracted with DCM (2 x 10ml). The organic layer was then dried with $MgSO_4$, filtered and evaporated to give the title compound (24mg, 73%).

^{1}H NMR 400MHz, $CDCl_3$) 2.15 (3H, s), 4.72 (2H, s), 6.13 (1H, d, J=2Hz), 6.29 (1H, d, J=3Hz), 6.59 (1H, d, J=8Hz), 6.96-7.06 (3H, m), 7.09 (1H, dd, J=2,8Hz), 7.22-7.33 (5H,m), 7.64 (1H,d, J=2Hz).

LC/MS t=4.26 min, [MH+] 452/454/456.

<u>Example 40 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-5-bromobenzoic acid</u>

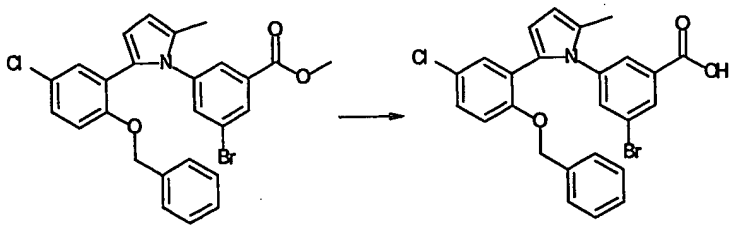
a) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-5-bromobenzoic acid methyl ester

Procedure as for 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester, using 3-amino-5-bromo-benzoic acid methyl ester (ex. SALOR) to give the title compound (35mg, 38%).

^{1}H NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 3.82 (3H, s), 4.74 (2H, s), 6.12 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.60 (1H, d, J=9Hz), 7.04-7.11 (3H, m), 7.24-7.32 (5H, m), 7.60 (1H, s), 8.02 (1H, s).

LC/MS t=4.26 min [MH+] 510/512/514.

b) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-5-bromobenzoic acid



Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chlorobenzoic acid, to give title compound (34mg, 100%).

^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.74 (2H, s), 6.13 (1H, d, J=3Hz), 6.3 (1H, d, J=3Hz), 6.61 (1H, d, J=9Hz), 7.4-7.12(3H, m), 7.23-7.35 (5H,m), 7.60, (1H, s), 8.06 (1H, s).

LC/MS t=4.30 min [MH+] 496/498/500.

Example 41 3-{2-[5-Chloro-2-(4-fluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-5-acetylamino-benzoic acid

a) 5-Chloro-2-(4-fluoro-benzyloxy)-benzaldehyde

Procedure as for 2-benzyloxy-5-chloro-benzaldehyde to give the title compound.

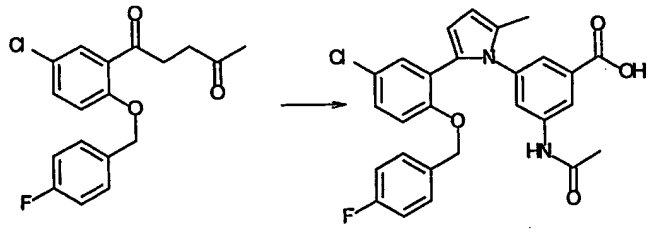
LCMS t=3.56 min[MNH_4^+] 282

b) 1-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione

Procedure as for 1-(2-benzyloxy-5-chloro-phenyl)-pentane-1,4-dione to give the title compound.

LCMS rt=3.46

c) 3-{2-[5-Chloro-2-(4-fluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-5-acetylamino-benzoic acid

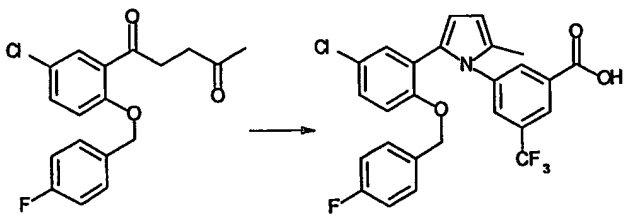


Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the apropriate amine (Hakansson *et al*, US3907880), to give the title compound (35mg, 14%).

^{1}H NMR (400MHz, $CDCl_3$) 2.14 (3H, s), 2.16 (3H, s), 4.71 (2H, s), 5.98 (1H, d, J=3Hz), 6.12 (1H,d, J=3Hz), 6.57 (1H, d, J=8Hz), 6.93-7.10 (5H, m), 7.18-7.25 (2H, m), 7.44 (1H, s), 7.48 (1H, s).

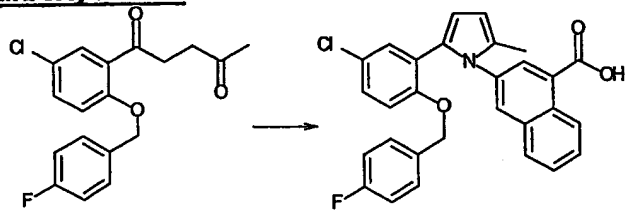
LC/MS t=3.66 min, [MH+] 493/495.

Example 42 3-{2-[5-Chloro-2-(4-fluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-5-trifluoromethyl benzoic acid



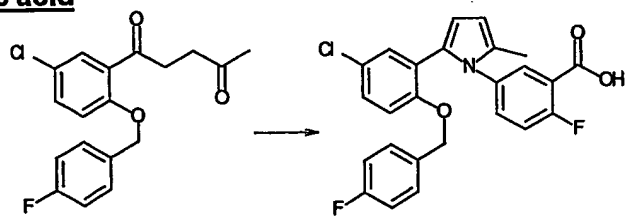
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (70mg, 28%).
^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.64 (2H, s), 6.16 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.58 (1H, d, J=3Hz), 6.92-7.06 (4H, m), 7.12 (1H, dd, J=2,8Hz), 7.3 (1H, d, J=2.4Hz), 7.40 (1H,s), 7.85 (1H, s), 8.17 (1H, s).
LC/MS t=4.25 min [MH+] 504/506.

Example 43 3-{2-[5-Chloro-2-(4-fluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}naphthalene-1-carboxylic acid



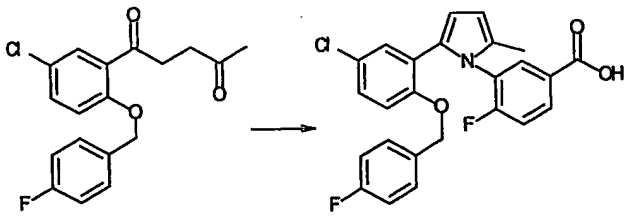
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine (Ruminski *et al*, WO9708145) to give the title compound (70mg, 30%).
^{1}H NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 4.60 (2H, s), 6.18 (1H, d, J=3Hz), 6.33 (1H, d, J=3Hz), 6.46 (1H, d, J=8Hz), 6.82-6.92 (4H, m), 7.03 (1H, dd, J=2.5, 9Hz), 7.39 (1H, d, J=2.5Hz), 7.49-7.56 (1H, m), 7.58 (1H, d, J=2Hz), 7.62-7.68 (2H, m), 8.06 (1H, d, J=2Hz), 9.02 (1H, d, J=9Hz).
LC/MS t=4.15 min [MH+] 486/488.

Example 44 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid



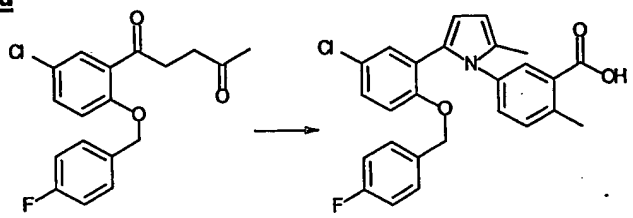
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (80mg, 35%).
^{1}H NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 4.70 (2H, s),6.12 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.60 (1H, d, J=9Hz), 6.93-7.02 (3H, m), 7.02-7.12 (5H, m), 7.64 (1H, dd, J=2.5, 7Hz).
LC/MS t=4.02 min [MH+] 454/456.

Example 45 3-{2-[5-Chloro-2-(4-fluorobenzyloxy)-phenyl]-5-methylpyrrole-1-yl}-4-fluorobenzoic acid



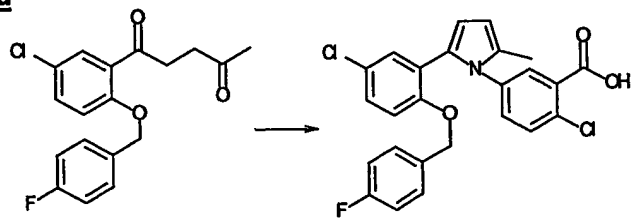
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (110mg, 48%).
LC/MS t=3.96 min [MH+] 454.

Example 46 3-{2-[5-Chloro-2-(4-fluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-methyl-benzoic acid



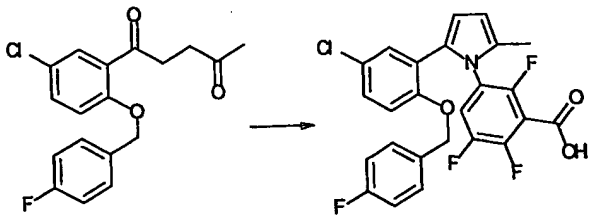
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine (Ashton *et al, J. Med. Chem.*, 1996, 39(17), 3343-3356, to give the title compound (30mg, 26%).
^{1}H NMR (400MHz, $CDCl_3$) 2.14 (3H, s), 2.62 (3H, s), 4.71 (2H, s), 6.12 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.57 (1H, d, J=8Hz), 6.92-7.12 (7H, m), 7.24 (1H, d, J=2Hz), 7.72 (1H, d, J=2Hz).
LC/MS t=4.04min [MH+] 450/452.

Example 47 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid



Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (50mg, 21%).
^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 4.68 (2H, s), 6.13 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.58 (1H, d, J=8Hz), 6.95-7.05 (5H, m), 7.10 (1H, dd, J=2, 8Hz), 7.24-7.32 (2H, m), 7.62 (1H, d, J=2Hz).
LC/MS t=4.24min [MH+] 470/472/474.

Example 48 3-{2-[5-Chloro-2-(4-fluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-2,5,6-trifluorobenzoic acid



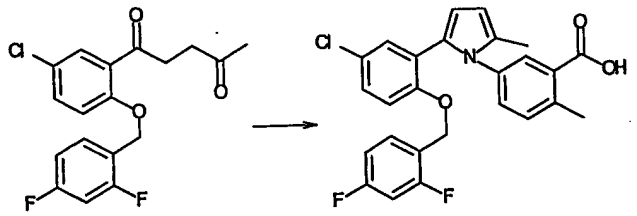
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (20mg, 8%).
^{1}H NMR (400MHz, $CDCl_3$) 2.10 (3H, s), 4.78 (2H, s), 6.13 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.64 (1H, d, J=8Hz), 6.86-7.03 (4H, m), 7.03-7.15 (3H, m).
LC /MS t=4.59 min [MH+] 490/492.

Example 49 3-{2-[5-Chloro-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-methyl-benzoic acid

a) 5-Chloro-2-(2,4-difluoro-benzyloxy)-benzaldehyde
Procedure as for 2-benzyloxy-5-chloro-benzaldehyde to give the title compound.
LCMS t=3.60 min.

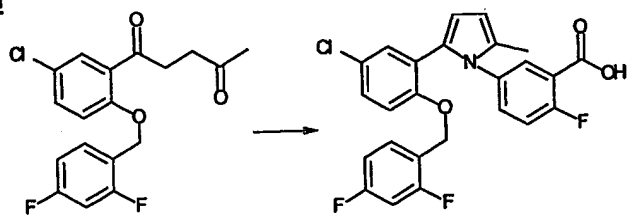
b) 1-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione
Procedure as for 1-[5-chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione to give the title compound.
LCMS t=3.49 min [MNa^+] 375

c) 3-{2-[5-Chloro-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-methyl-benzoic acid



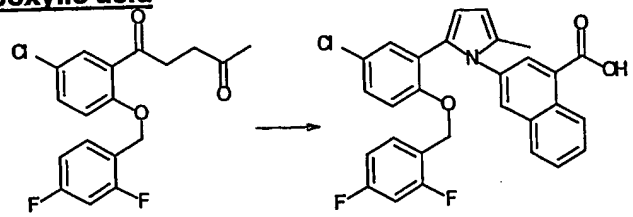
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (45mg, 20%).
^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 2.62 (3H, s), 4.76 (2H, s), 6.12 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.61 (1H,d J=9Hz), 6.72-6.82 (2H, m), 6.94-7.0 (2H, m), 7.05-7.14 (2H,m), 7.20 (1H, d, J=2.4Hz), 7.74 (1H, d, J=2Hz).
LC/MS t=4.07 min [MH+] 468/470.

Example 50 3-{2-[5-Chloro-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-fluoro-benzoic acid



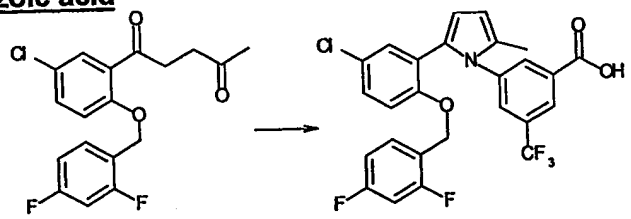
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (30mg, 13%).
^{1}H NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 4.76 (2H, s), 6.12 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.65 (1H, d, J=9Hz), 6.74-6.87 (2H, m) 6.97-7.07 (2H, m), 7.07-7.15 (2H, m), 7.22 (1H, d, J=2Hz), 7.68 (1H, dd, J=2, 7Hz).
LC/MS t=4.07 min [MH+] 472.

Example 51 3-{2-[5-Chloro-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-naphthalene-1-carboxylic acid



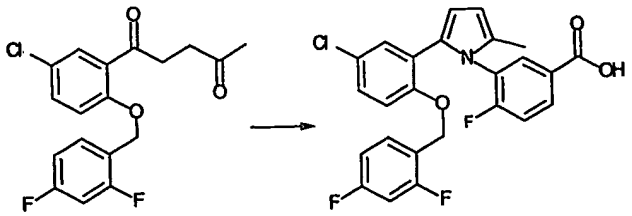
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (60mg, 24%).
^{1}H NMR (400MHz, $CDCl_3$) 2.20, (3H, s), 4.69 (2H, s), 6.18 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.51 (1H, d, J=8Hz), 6.58-6.65 (1H, m), 6.69-6.82 (2H, m), 7.05 (1H, dd, J=2.4,8Hz), 7.36 (1H, d, J=2.4Hz), 7.50-7.56 (1H, m), 7.60-7.70 (3H, m), 8.10 (1H, d, J=2Hz), 9.03(1H, d, J=8Hz).
LC/MS t=4.22 min [MH+] 504/506.

Example 52 3-{2-[5-Chloro-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-5-trifluoromethylbenzoic acid



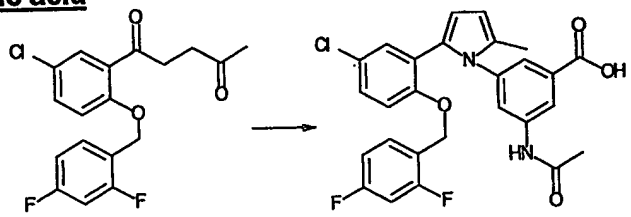
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (18mg, 7%).
^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.70 (2H, s), 6.16 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.62 (1H, d, J=8Hz), 6.73-6.84 (2H, m), 6.92-7.01 (1H, m), 7.13 (1H, dd, J=2.4, 8Hz), 7.28 (1H, d, J=2Hz), 7.42 (1H, s), 7 86 (1H, s), 7.95 (1H, s).
LC/MS t=5.28 min [MH+] 522/524.

Example 53 3-{2-[5-Chloro-2-(2,4-difluorobenzyloxy)phenyl]-5-methylpyrrol-1-yl}-4-fluorobenzoic acid



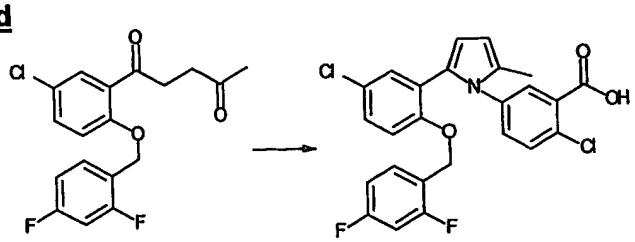
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (60mg, 25%).
^{1}H NMR (400MHz, $CDCl_3$) 2.10 (3H, s), 4.82 (2H, d, J=2Hz), 6.1 (1H, d J=3Hz), 6.31 (1H, d, J=3Hz), 6.61 (1H, d, J=8Hz), 6.74-6.83 (2H, m), 7.00-7.09 (2H, m), 7.12 (1H, t, J=7Hz), 7.2 (1H, d, J=2Hz), 7.77 (1H, dd, J=2, 7Hz), 7.98-8.45 (1H, m).
LC/MS t=4.01 min [MH+] 472/474.

Example 54 3-{2-[5-Chloro-2-(2,4-difluorobenzyloxy)phenyl]-5-methylpyrrol-1-yl}-5-acetylamino-benzoic acid



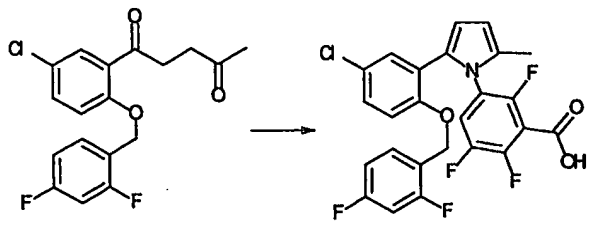
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (60mg, 23%).
^{1}H NMR (400MHz, $CDCl_3$) 2.26 (3H,s), 2.15 (3H, s), 2.16 (3H,s) 4.78 (2H, s), 6.11 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.62 (1H, d, J=8Hz), 6.72-6.84 (2H, m), 7.00-7.08 (2H, m), 7.20 (1H, d, J=2Hz), 7.46 (1H, s), 7.60 (1H, s), 7.95 (1H, s).
LC/MS t=3.71 min [MH+] 511/513.

Example 55 3-{2-[5-Chloro-2-(2,4-difluorobenzyloxy)phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid



Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (45mg, 18%).
^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.76 (2H, s), 6.13 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.64 (1H, d, J=9Hz), 6.75-6.85 (2H, m), 6.90-6.98 (2H, m), 7.02 (1H, dd, J=2, 8Hz), 7.12 (1H, dd, J=2, 8Hz), 7.30 (1H, d, J=8Hz), 7.65 (1H, d, J=2Hz).
LC/MS t=4.25 min [MH+] 488/490/492.

Example 56 3-{2-[5-Chloro-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-2,5,6-trifluorobenzoic acid



Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (27mg, 10%).
^{1}H NMR (400MHz, $CDCl_3$) 2.10 (3H, s), 4.84 (2H, dd, J=7, 20Hz), 6.30 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.68 (1H, d, J=8Hz), 6.74-6.82 (2H, m), 6.89-6.99 (1H, m), 6.99-7.08 (1H, m), 7.14 (1H, dd, J=2, 9Hz), 7.25 (1H, d, 2Hz).
LC/MS t=4.64 min [MH+] 508/510.

Example 57 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)phenyl]-5-methylpyrrol-1-yl}-6-chlorobenzoic acid

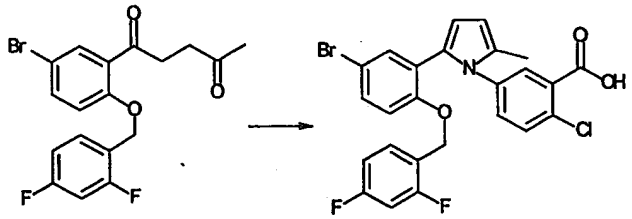
a) 5-Bromo-2-(2,4-difluoro-benzyloxy)-benzaldehyde

Procedure as for 2-benzyloxy-5-chloro-benzaldehyde to give the title compound.
LCMS t=3.71 min [MNa^+] 349/351.

b) 1-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione

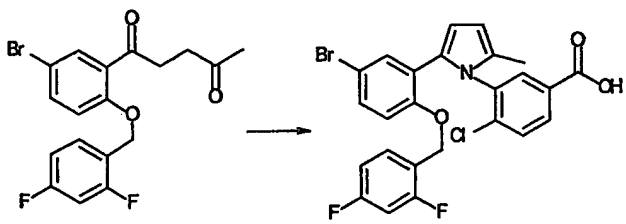
Procedure as for 1-[5-chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione to give the title compound.
LCMS t=3.41 min [MH^+] 397/399.

c) 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)phenyl]-5-methylpyrrol-1-yl}-6-chlorobenzoic acid



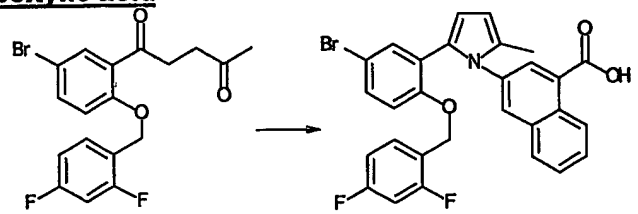
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (80mg, 30%).
^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 4.75 (2H, s), 6.12 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.58 (1H, d, J=8Hz), 6.74-6.85 (2H, m), 6.89-6.97 (1H,m), 7.01 (1H, dd, J=2, 8Hz), 7.23-7.29 (1H, m), 7.32 (1H, d, J=8Hz), 7.42 (1H, d, J=2Hz), 7.66 (1H, d, J=2Hz).
LC/MS t=4.25 min [MH+] 532/534/536.

Example 58 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-4-chlorobenzoic acid



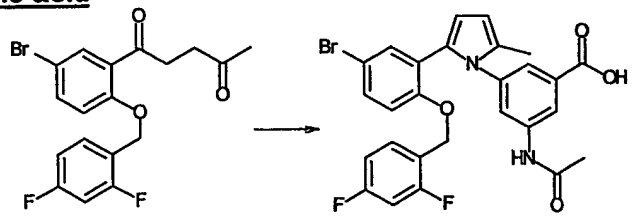
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (125mg, 47%).
LC/MS t=4.24 min [MH+] 532/534/536.

Example 59 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-naphthalene-1-carboxylic acid



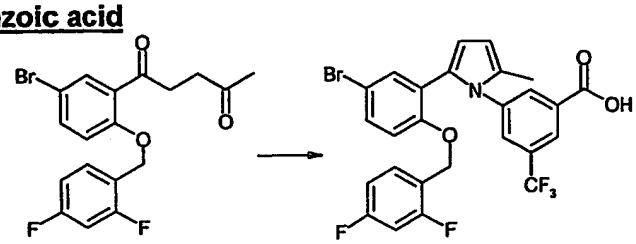
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, with 4Å molecular sieve (~0.5g) to give the title compound (25mg, 91%).
^{1}H NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 4.68 (2H, s), 6.18 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.45 (1H, d, J=9Hz), 6.56-6.64 (1H, m), 6.68-6.79 (2H, m), 7.19 (1H, dd, J=2, 8Hz), 7.49-7.58 (2H, m), 7.58-7.72 (3H, m), 8.09 (1H, d, J=2Hz), 9.03 (1H, d, J=8Hz).
LC/MS t=4.26 min [MH+] 548/550.

Example 60 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-5-acetylamino-benzoic acid



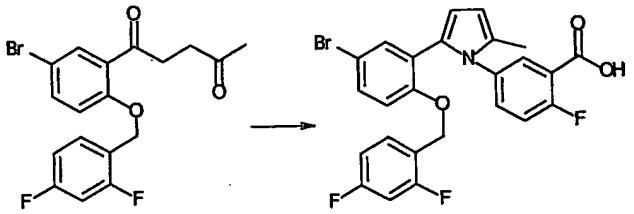
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, with 4Å molecular sieves (~0.5g) to give the title compound (25mg, 90%).
^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s),2.16 (6H, s), 4.77 (2H, s), 6.11 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.56 (1H, d, J=8Hz), 6.71-6.84 (2H, m), 6.98-7.06 (1H, m), 7.18 (1H, dd, J=2, 9Hz), 7.35 (2H, d, J=2Hz), 7.45 (1H, s), 7.58 (1H, s), 7.97 (1H, s).
LC/MS t=3.76 min [MH+] 555/557.

Example 61 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)phenyl]-5-methylpyrrol-1-yl}-5-trifluoromethylbenzoic acid



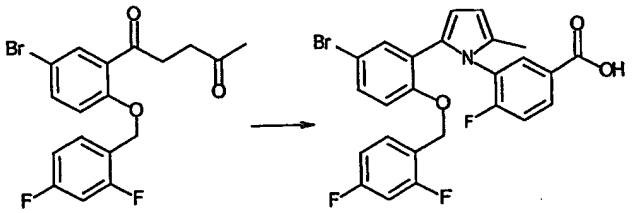
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (44mg, 16%).
LC/MS t=4.33 min [MH+] 566/568.

Example 62 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-fluorobenzoic acid



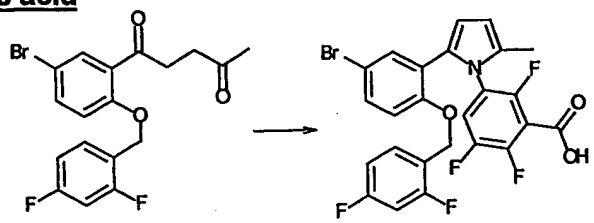
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (40mg, 15%).
^{1}H NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 4.77 (2H, s), 6.12 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.60 (1H, d, J=8Hz), 6.76-6.84 (2H, m), 6.97-7.06 (2H, m), 7.08-7.15 (1H, m), 7.24 (1H, d, J=2Hz), 7.37 (1H, d, J=2Hz), 7.67 (1H, dd, J=2, 7Hz).
LC/MS t=4.10 min [MH+] 516/518.

Example 63 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-4-fluorobenzoic acid



Procedure as for 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, to give the title compound (53mg, 20%).
^{1}H NMR(400MHz, $CDCl_3$) 2.10 (3H, s), 4.83 (2H, s), 6.15 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.56 (1H, d, J=9Hz), 6.73 (2H, m), 6.99-7.08 (1H, m), 7.21 (1H, dd, J=2, 9Hz), 7.85-7.17 (1H, m), 7.35 (1H, d, J=2Hz), 7.77 (1H, dd, J=2, 7Hz), 7.98-8.05 (1H, m).
LC/MS t=4.06 min [MH+] 516/518.

Example 64 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-2,5,6-trifluorobenzoic acid



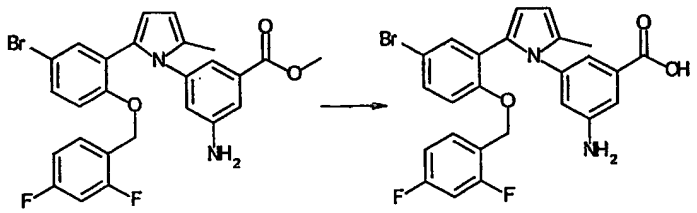
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, with 4Å molecular sieve (~0.5g) to give the title compound (70mg, 25%).
LC/MS t=4.65 min [MH+] 552/554.

Example 65 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-5-Amino-benzoic acid

a) 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-5-amino-benzoic acid methyl ester

Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester using the appropriate amine, with 4Å molecular sieve (~0.5g) to give the title compound (73mg, 70%).
^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 3.82 (3H, s), 4.99 (2H, s), 6.08 (1H, d J=3Hz), 6.27 (1H, d, J=3Hz), 6.42 (1H, t, J=2, 4Hz), 6.58 (1H, d, J=8Hz), 6.75-6.84 (2H, m), 7.01-7.09 (1H, m), 7.11 (1H, s), 7.18-7.24 (2H,m), 7.33 (1H, d J=2Hz).
LC/MS t=3.96 min [MH+] 527/529.

b) 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-5-Amino-benzoic acid



Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chloro-benzoic acid methyl ester, to give the title compound (48mg, 33%).
^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.80 (2H, s), 6.09 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.45 (1H, s), 6.59 (1H, d, J=9Hz), 6.73-6.84 (2H, m), 7.02-7.10 (1H, m), 7.17 (1H, s), 7.19-7.29 (2H, m), 7.34 (1H, d, J=2Hz).
LC/MS t=3.77 min [MH+] 513/515.

Example 66 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-5-(2-oxopyrrolidin-1-yl)-benzoic acid

a) 3-Nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester

3-Bromo-5-methyl-benzoic acid methyl ester (2.48g, 10mmol) (South *et al*, WO0187854), 2-pyrrolidinone (0.89ml, 12mmol), caesium carbonate (4.8g, 14mmol), palladium bis(dibenzylideneacetone) (190mg, 0.2mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (400mg, 0.7mmol), and caesium carbonate (4.8g, 14.8mmol) were heated at reflux, under nitrogen for 3 hours. The reaction mixture was then cooled and filtered through Celite® and washed through with CH_2Cl_2 (100ml). The mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel with isohexane/Et_2O (20-80%) then MeOH/Et_2O (98%) as eluant, to give the title compound (2.0g, 76%).

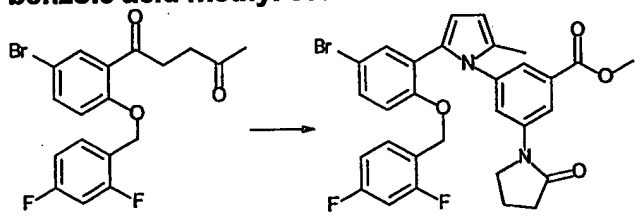
^{1}H-NMR (400MHz, $CDCl_3$) 2.36 (2H, dt, J=8Hz), 2.70 (2H, t, J=8Hz), 3.97 (2H, t, J=8Hz), 3.99 (3H, s), 8.55 (1H, t, J=2Hz), 8.62 (1H, t, J=2Hz), 8.86 (1H, t, J=2Hz).
LC/MS t=2.78 min [MH^+] 265.

b) 3-Amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester

3-Nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (2.0g, 7.6mmol) and Raney nickel (0.5g) in methanol (70ml) were stirred under a hydrogen atmosphere at room temperature for 3 hours. The mixture was cooled and the catalyst was filtered off through a pad of Celite□ and washed through with MeOH/CH_2Cl_2 (2.5:1, 1L). The mixture was concentrated *in vacuo* to yield the title compound as a white solid (1.6g, 90%).

^{1}H-NMR (400MHz, DMSO) 2.03 (2H, dt, J=8Hz), 2.47 (2H, t, J=8Hz), 3.77 (2H, t, J=8Hz), 3.80 (3H, s), 5.39 (2H, broad s), 6.96 (1H, s), 7.14 (1H, s), 7.36 (1H, s).
LC/MS t=2.19 min [MH^+] 235.

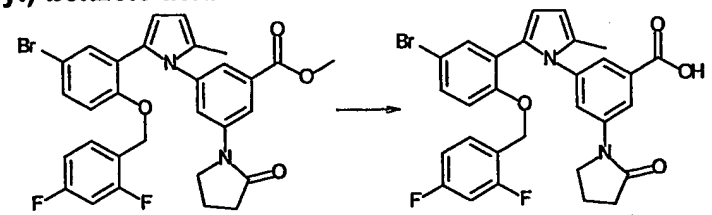
c) 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl]-5-(2-oxopyrrolidin-1-yl)-benzoic acid methyl ester



1-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-pentane-1,4-dione (200mg, 0.5mmol), was treated with 3-amino-5-(2-oxopyrrolidin-1-yl)-benzoic acid methyl ester (117mg, 0.5mmol), and *p*-toluenesulfonic acid (~50mg) and 4Å molecular sieve powder (~0.5g) in N-methylpyrrolidinone(3ml). The reaction mixture was then heated at 180°C over 18hrs under nitrogen. The mixture was cooled, concentrated to an oil at 80°C, diluted with EtOAc (7ml) and filtered through Celite®, washing through with EtOAc (10ml). The filtrate was then washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was purified by chromatography on silica gel with an isohexane / EtOAc gradiant system giving the title compound (60mg, 20%).

^{1}H NMR (400MHz, $CDCl_3$) 2.07-2.16 (2H, m), 2.18 (3H, s), 2.57 (2H, t J=8Hz), 3.64 (2H, t, J=8Hz), 3.85 (3H, s), 4.77 (2H, s), 6.12 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.56 (1H, d, J=8.5Hz), 6.73-6.83 (2H, m), 6.93-7.25 (1H, m), 7.22 (1H, dd, J=2, 8.5Hz), 7.37 (1H, d, J=2Hz), 7.46 (1H, s), 7.61 (1H, s), 8.09 (1H, s).
LC/MS t=4.00 min [MH+] 595/597.

d) 3-{2-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-5-methylpyrrol-1-yl}-5-(2-oxopyrrolidin-1-yl)-benzoic acid



Procedure as for 3-{[2-[5-chloro-2-(benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-chlorobenzoic acid, to give the title compound (50mg, 86%).

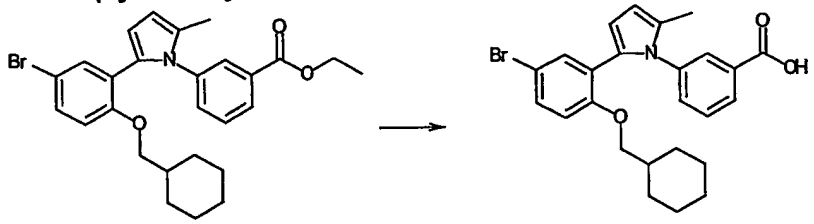
^{1}H NMR (400MHz, $CDCl_3$) 2.08-2.17 (2H, m), 2.19 (3H, s), 2.58 (2H, t, J=8Hz), 3.66 (2H, t, J=8Hz), 4.78 (2H, s), 6.12 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.56 (1H, d, J=8.5Hz), 6.71-6.83 (2H, m), 6.96-7.03 (1H, m), 7.22 (1H, dd, J=2, 8.4Hz), 7.38 (1H, d, J=2Hz), 7.50 (1H, s), 7.69 (1H, s), 8.10 (1H, s).
LC/MS t=3.84 min [MH+] 581/583.

Example 67 3-{2-[5-Bromo-2-(cyclohexylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(cyclohexylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Cyclohexylmethyl bromide (146mg, 0.83mmol) was added to 3-[2-(5-bromo-2-hydroxy-phenyl)-5-methyl-pyrrol-1-yl]-benzoic acid ethyl ester (220mg, 0.55mmol) and K_2CO_3 (152mg, 1.1mmol) in DMF (2ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel using isohexane / EtOAc (5%) as eluant, to give the title compound (179mg, 66%).
^{1}H-NMR (400MHz, $CDCl_3$) 0.79-0.92 (2H, m), 1.08-1.29 (3H, m), 1.38 (3H, t, J=7Hz), 1.60-1.73 (6H, m), 2.19 (3H, s), 3.40 (2H. d, J=7Hz), 4.36 (2H, q, J=7Hz), 6.11 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.54 (1H, d, J=9Hz), 7.15-7.22 (2H, m), 7.25 (1H, d, J=3Hz), 7.32 (1H, t, J=8Hz), 7.83 (1H, t, J=1Hz), 7.92 (1H, dt, J=1Hz, 8Hz).
LC/MS t=4.51 min [MH^+] = 496.

b) 3-{2-[5-Bromo-2-(cyclohexylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Bromo-2-(cyclohexylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (150mg, 0.3mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (129mg, 91%).
^{1}H-NMR (400MHz, $CDCl_3$) 0.79-0.92 (2H, m), 1.09-1.29 (3H, m), 1.59-1.73 (6H, m), 2.19 (3H, s), 3.41 (2H. d, J=7Hz), 6.11 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.54 (1H, d, J=9Hz), 7.19-7.25 (3H, m), 7.35 (1H, t, J=8Hz), 7.91 (1H, broad s), 7.98 (1H, d, J=8Hz).
LC/MS t=4.33 min[MH^+] = 468.

Example 68 3-{2-[5-Methanesulfonyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 5-Methanesulfonyl-2-(4-methoxy-benzyloxy)-benzaldehyde

4-Methoxybenzyl chloride (4.09g, 0.026mol) was added to 2-hydroxy-5-methanesulfonyl-benzaldehyde (3.48g, 0.017mol) {prepared *via* the method of Suzuki *et al*, *Chem. Pharm.*

Bull., 1989, 31 (5), 1751} and K_2CO_3 (4.8 g, 0.035 mol) in DMF (35 ml). The mixture was heated to 60°C for 3 hours. The reaction mixture was quenched with water (250 ml) and washed with EtOAc (2 x 250ml). The organic extracts were combined and washed with brine (150ml), dried ($MgSO_4$) filtered and concentrated to give the title compound (6.5g, 100%).

^{1}H-NMR (400MHz, *d*6-DMSO) F5778 3.77 (3H, s), 5.35 (2H, s), 6.96 (2H, d, J=9Hz), 7.47 (2H, d, J=9Hz), 7.59 (1H, d, J=10Hz), 8.14-8.19 (2H, m).

LC/MS t=2.94 min [MNH_4^+] = 338.

b) 1-[5-Methanesulfonyl-2-(4-methoxy-benzyloxy)-phenyl]-pentane-1,4-dione

Methyl vinyl ketone (1.72ml, 20mmol) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (1.54g, 6mmol) were added to 5-methanesulfonyl-2-(4-methoxy-benzyloxy)-benzaldehyde (6.5g, 20mmol) in EtOH (5.5ml) and triethylamine (8.5ml, 60mmol). The mixture was heated at 100°C for 18 hours. The reaction mixture was quenched with saturated NH_4Cl solution (300 ml) and washed with EtOAc (2 x 250ml). The organic extracts were combined and washed with saturated $NaHCO_3$ solution (250 ml) and brine (200 ml), dried ($MgSO_4$) filtered and concentrated. The crude product was purified by chromatography on silica gel (50% EtOAc/iso-hexane) to give the title compound (2.92 g, 37 %).

^{1}H-NMR (400MHz, *d*6-DMSO) 2.09 (3H, s), 2.73 (2H, t, J=6Hz), 3.10 (2H, t, J=6Hz), 3.77 (3H, s), 5.30 (2H, s), 6.97 (2H, d, J=9Hz), 7.47 (2H, d, J=9Hz), 7.53 (1H, d, J=9Hz), 8.04-8.08 (2H, m).

LC/MS t=2.92 min [MNH] = 389.

c) 3-{2-[5-Methanesulfonyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

1-[5-Methanesulfonyl-2-(4-methoxy-benzyloxy)-phenyl]-pentane-1,4-dione (2.91g, 7.5mmol), ethyl-3-aminobenzoate (1.6ml, 10.7mmol) and *para*-toluenesulfonic acid (0.22g, 1.2mmol) were heated at reflux in toluene (75ml) for 16 hours. Upon cooling, the mixture was concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (40%) as eluant, to give the title compound (2.22g, 74%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.37 (3H, t, J=7Hz), 2.18 (3H, s), 2.68 (3H, s), 4.35 (2H, q, J=7Hz), 6.21 (1H, d, J=3Hz), 6.44 (1H, d, J=3Hz), 6.56 (1H, s), 7.02 (1H, d, J=9Hz), 7.28-7.30 (2H, m), 7.43 (1H, t, J=8Hz), 7.63 (1H, dd, J=2Hz, 9Hz), 7.77 (1H, t, J=1Hz), 7.99 (1H, dt, J=1Hz, 8Hz).

LC/MS t=3.17 min [MH^+] = 400.

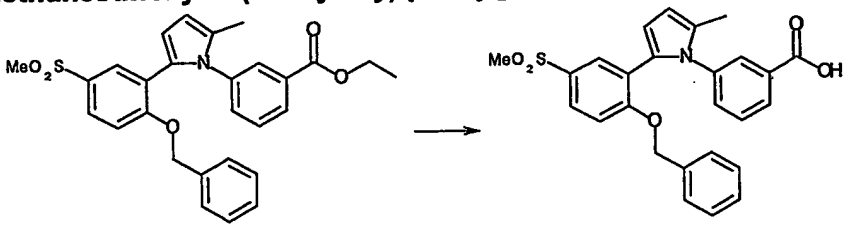
d) 3-{2-[5-Methanesulfonyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Benzyl bromide (0.089ml, 0.75mmol) was added to 3-{2-[5-Methanesulfonyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200mg, 0.50mmol) and K_2CO_3 (138mg, 1.0mmol) in DMF (2ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (30%) as eluant, to give the title compound (218mg, 89%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7Hz), 2.17 (3H, s), 2.88 (3H, s), 4.28 (2H, q, J=7Hz), 4.91 (2H, s), 6.15 (1H, d, J=3Hz), 6.42 (1H, d, J=3Hz), 6.79 (1H, d, J=9Hz), 7.10-7.15 (2H, m), 7.16-7.19 (1H, m), 7.28-7.34 (4H, m), 7.65 (1H, dd, J=2Hz, 8Hz), 7.70 (1H, d, J=2Hz), 7.73 (1H, t, J=1Hz), 7.99 (1H, d, J=8Hz).

LC/MS t=3.68 min [MH^+] = 490.

e) 3-{2-[5-Methanesulfonyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{[2-[5-Methanesulfonyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200mg, 0.4mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (177mg, 95%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 2.90 (3H, s), 4.91 (2H, s), 6.17 (1H, d, J=3Hz), 6.42 (1H, d, J=3Hz), 6.80 (1H, d, J=9Hz), 7.10-7.14 (2H, m), 7.20-7.25 (1H, m), 7.28-7.38 (4H, m), 7.66 (1H, dd, J=2Hz, 8Hz), 7.72 (1H, d, J=2Hz), 7.75 (1H, t, J=1Hz), 7.97 (1H, d, J=8Hz).

LC/MS t=3.40 min [MH^+] = 462.

Example 69 3-{2-[5-Methanesulfonyl-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

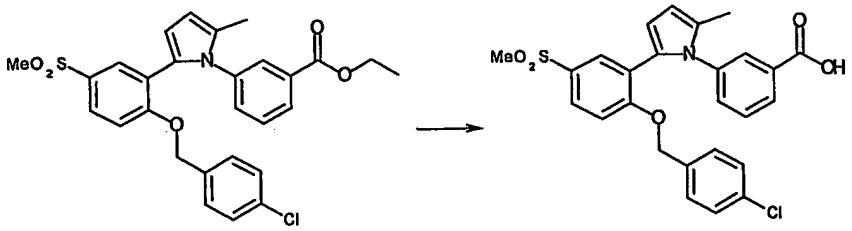
a) 3-{2-[5-Methanesulfonyl-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

4-Chloro-benzyl bromide (154mg, 0.75mmol) was added to 3-{2-[5-methanesulfonyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200mg, 0.50mmol) and K_2CO_3 (138mg, 1.0mmol) in DMF (2ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (30%) as eluant, to give the title compound (205mg, 78%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7Hz), 2.17 (3H, s), 2.89 (3H, s), 4.29 (2H, q, J=7Hz), 4.87 (2H, s), 6.16 (1H, d, J=3Hz), 6.41 (1H, d, J=3Hz), 6.77 (1H, d, J=9Hz), 7.05 (2H, d, J=8Hz), 7.16-7.19 (1H, m), 7.28-7.34 (3H, m), 7.67 (1H, dd, J=2Hz, 8Hz), 7.70-7.73 (2H, m), 7.92 (1H, d, J=8Hz).

LC/MS t=3.84 [MH^+] = 524/526.

b) 3-{2-[5-Methanesulfonyl-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-methanesulfonyl-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200mg, 0.4mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (164mg, 87%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 2.90 (3H, s), 4.86 (2H, s), 6.16 (1H, d, J=3Hz), 6.41 (1H, d, J=3Hz), 6.77 (1H, d, J=9Hz), 7.07 (2H, d, J=8Hz), 7.20-7.24 (1H, m), 7.29 (2H, d, J=8Hz), 7.36 (1H, t, J=8Hz), 7.68 (1H, dd, J=2Hz, 8Hz), 7.72 (2H, d, J=2Hz), 7.98 (1H, d, J=8Hz).

LC/MS t=3.59 min [MH^+] = 496/498.

Example 70 3-{2-[5-Methanesulfonyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

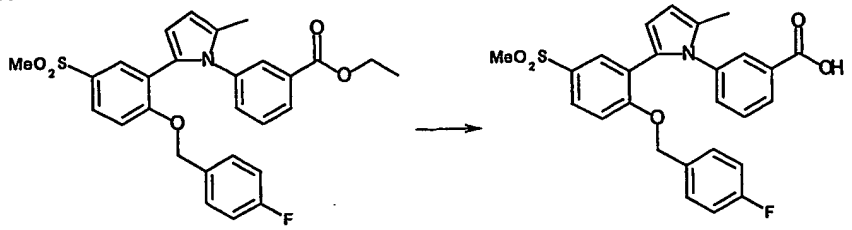
a) 3-{2-[5-Methanesulfonyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

4-Fluoro-benzyl bromide (142mg, 0.75mmol) was added to 3-{2-[5-methanesulfonyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200mg, 0.50mmol) and K_2CO_3 (138mg, 1.0mmol) in DMF (2ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel, with isohexane / EtOAc (30%) as eluant, to give the title compound (229mg, 90%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7Hz), 2.17 (3H, s), 2.88 (3H, s), 4.29 (2H, q, J=7Hz), 4.86 (2H, s), 6.14 (1H, d, J=3Hz), 6.41 (1H, d, J=3Hz), 6.79 (1H, d, J=9Hz), 6.99-7.05 (2H, m), 7.08-7.14 (2H, m), 7.15-7.17 (1H, m), 7.32 (1H, t, J=8Hz), 7.65-7.71 (3H, m), 7.92 (1H, d, J=8Hz).

LC/MS t=3.70 min [MNH_4^+] = 525.

b) 3-{2-[5-Methanesulfonyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Methanesulfonyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200mg, 0.4mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl

acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (173mg, 92%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 2.90 (3H, s), 4.87 (2H, s), 6.15 (1H, d, J=3Hz), 6.41 (1H, d, J=3Hz), 6.80 (1H, d, J=9Hz), 6.99-7.05 (2H, m), 7.09-7.14 (2H, m), 7.19-7.23 (1H, m), 7.36 (1H, t, J=8Hz), 7.67 (1H, dd, J=2Hz, 8Hz), 7.72 (2H, d, J=2Hz), 7.97 (1H, d, J=8Hz).

LC/MS t=3.42 min [MH^+] = 480.

Example 71 3-{2-[5-Methanesulfonyl-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

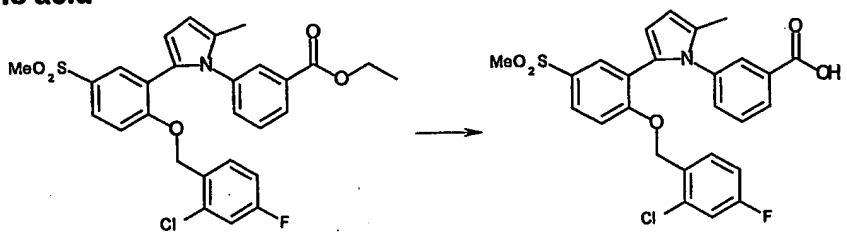
a) 3-{2-[5-Methanesulfonyl-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

2-Chloro-4-fluoro-benzyl bromide (168mg, 0.75mmol) was added to 3-{2-[5-methanesulfonyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200mg, 0.50mmol) and K_2CO_3 (138mg, 1.0mmol) in DMF (2ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (30%) as eluant, to give the title compound (248mg, 91%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7Hz), 2.18 (3H, s), 2.89 (3H, s), 4.29 (2H, q, J=7Hz), 4.93 (2H, s), 6.16 (1H, d, J=3Hz), 6.42 (1H, d, J=3Hz), 6.79 (1H, d, J=9Hz),6.94 (1H, ddd, J=2Hz, 8Hz), 7.00-7.16 (1H, m), 7.13 (1H, dd, J=2Hz, 8Hz), 7.18-7.22 (1H, m), 7.34 (1H, t, J=8Hz), 7.67-7.73 (3H, m), 7.93 (1H, d, J=8Hz).

LC/MS t=3.84 min [MNH_4^+] = 559/561.

b) 3-{2-[5-Methanesulfonyl-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Methanesulfonyl-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200mg, 0.4mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (170mg, 90%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 2.90 (3H, s), 4.93 (2H, s), 6.17 (1H, d, J=3Hz), 6.42 (1H, d, J=3Hz), 6.80 (1H, d, J=9Hz), 6.94 (1H, ddd, J=2Hz, 8Hz), 7.03-7.08 (1H, m), 7.12 (1H, dd, J=2Hz, 8Hz), 7.25-7.27 (1H, m), 7.39 (1H, t, J=8Hz), 7.69-7.75 (3H, m), 7.98 (1H, d, J=8Hz).

LC/MS t=3.57 min [MH^+] = 514/516.

Example 72 3-{2-[5-Methanesulfonyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

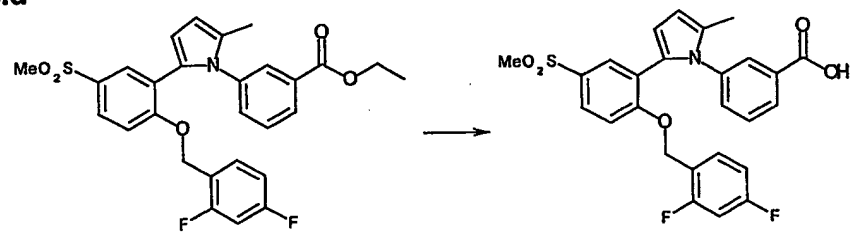
a) 3-{2-[5-Methanesulfonyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

2,4-Difluoro-benzyl bromide (156mg, 0.75mmol) was added to 3-{2-[5-methanesulfonyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200mg, 0.50mmol) and K_2CO_3 (138mg, 1.0mmol) in DMF (2ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (30%) as eluant, to give the title compound (233mg, 88%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.32 (3H, t, J=7Hz), 2.17 (3H, s), 2.88 (3H, s), 4.30 (2H, q, J=7Hz), 4.92 (2H, s), 6.14 (1H, d, J=3Hz), 6.40 (1H, d, J=3Hz), 6.80-6.87 (3H, m), 7.05-7.12 (1H, m), 7.18 (1H, d, J=8Hz), 7.34 (1H, t, J=8Hz), 7.68-7.72 (3H, m), 7.93 (1H, d, J=8Hz).

LC/MS t=3.71 min [MH^+] = 526.

b) 3-{2-[5-Methanesulfonyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Methanesulfonyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (200mg, 0.4mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (168mg, 89%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 2.90 (3H, s), 4.92 (2H, s), 6.16 (1H, d, J=3Hz), 6.40 (1H, d, J=3Hz), 6.80-6.87 (3H, m), 7.05-7.12 (1H, m), 7.18 (1H, d, J=8Hz), 7.36 (1H, t, J=8Hz), 7.68-7.73 (3H, m), 7.99 (1H, d, J=8Hz).

LC/MS t=3.44 min [MH^+] = 498.

Example 73 3-{2-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 2-Benzyloxy-5-trifluoromethyl-benzaldehyde

2-Hydroxy-5-trifluoromethyl-benzaldehyde (prepared *via* the procedure of *Schäfer, Synthesis* 2001, 15, 2259-2262) (0.5g, 2.63mmol), benzyl bromide (0.313ml, 3.95mmol) and potassium carbonate (0.727g, 5.26mmol) were heated in DMF (5ml) at 50°C in a nitrogen atmosphere for 1 hour. Upon cooling the reaction mixture was diluted with EtOAc and washed with sat. NH_4Cl. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were then washed with brine and

dried over $MgSO_4$, filtered and concentrated in vacuo. The resultant residue was purified by chromatography on silica gel eluting with 10% EtOAc/iso-hexane this yielded the title compound as a clear solid (0.14g, 19%).

^{1}H-NMR (400MHz, $CDCl_3$) 5.27 (2H, s), 7.15 (1H, d, J=9Hz), 7.32-7.48 (5H, m), 7.78 (1H, dd, J=3Hz, 9Hz) 8.12 (1H, d, J=3Hz) 10.60 (1H, s).

LC/MS t = 3.59 min.

b) 1-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-pentane-1,4-dione

2-Benzyloxy-5-trifluoromethyl-benzaldehyde (0.4g, 50% purity, 0.714mmol), triethylamine (0.3ml, 2.14mmol), methyl vinyl ketone (0.061ml, 0.728mmol) and 3-ethyl-5-(2-hydroxyethyl)-4-ethylthiazolium bromide (0.054g, 0.214mmol) were refluxed in EtOH (1.5ml) under a nitrogen atmosphere for 22 hours. Upon cooling the reaction mixture was diluted with EtOAc and washed with saturated NH_4Cl. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were then washed with saturated $NaHCO_3$ and brine and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with 10% EtOAc/iso-hexane. This yielded the title compound as an off white solid (0.057g, 23%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.19 (3H, s), 2.80 (2H, t, J=6Hz), 3.26 (2H, t, J=6Hz), 5.23 (2H, s), 7.10 (1H, d, J=9Hz), 7.35-7.46 (5H, m), 7.68 (1H, dd, J=3Hz, 9Hz), 8.02 (1H, d, J=3Hz).

LC/MS t = 3.51 min.

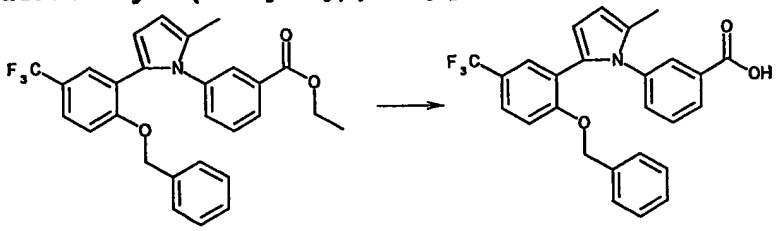
c) 3-{2-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

1-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-pentane-1,4-dione (1g, 2.86mmol) and ethyl-3-aminobenzoate (0.51ml, 3.43mmol) were heated in a sealed vessel at 150°C for 26 hours. Upon cooling the residue was purified by chromatography on silica gel eluting with 10% EtOAc/iso-hexane. This yielded the title compound as a yellow oil (0.77g, 56%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.29 (3H, t, J=7Hz), 2.17 (3H, s), 4.28 (2H, q, J=7Hz), 4.82 (2H, s), 6.15 (1H, d, J=3Hz), 6.37 (1H, d, J=3Hz), 6.70 (1H, d, J=9Hz), 7.05-7.08 (3H, m), 7.13 (1H, dt, J=1Hz, 8Hz), 7.28-7.35 (5H, m) 7.49 (1H, d, J=2Hz), 7.72 (1H, t, J=1Hz), 7.92 (1H, dt, J=1Hz, 8Hz).

LC/MS t = 4.19 min [MH^+] 480.

d) 3-{2-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.1g), 2M NaOH (3ml) and EtOH (5ml) were heated at 100°C in a sealed vessel for 45 minutes. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The

combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*, to yield the title compound as a brown solid (0.090g, 96%).
^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.84 (2H, s), 6.16 (1H, d, J=3Hz), 6.37 (1H, d, J=3Hz), 6.72 (1H, d, J=9Hz), 7.08 (2H, dd, J=1Hz, 9Hz), 7.17 (1H, broad d, J=9Hz), 7.28-7.36 (5H, m), 7.47 (1H, d, J=2Hz), 7.79 (1H, t, J=1Hz), 7.96 (1H, dt, J=1Hz, 8Hz).
LC/MS t=3.92 min [MH^+] 452.

Example 74 3-{2-[5-Trifluoromethyl-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

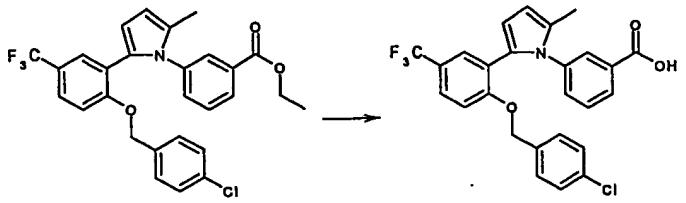
a) 3-{2-[5-Trifluoromethyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.65g, 1.36mmol), palladium on charcoal (10% containing 50% water) (0.13g, 20%w/w), ammonium formate (0.45g, 7.19mmol) and EtOH (9ml) were stirred at 60°C under a nitrogen atmosphere for 1.5 hours. Upon cooling the mixture was filtered and the solvent removed *in vacuo*. The residue was purified by chromatography on silica gel eluting with 10% EtOAc/iso-hexane to yield the title compound as a yellow oil (0.513g, 97%)
^{1}H-NMR (400MHz, $CDCl_3$) F7101 1.37 (3H, t, J=7Hz), 2.17 (3H, s), 4.35 (2H, q, J=7Hz), 6.18 (1H, d, J=3Hz), 6.28 (1H, s), 6.40 (1H, d, J=3Hz), 6.94 (1H, d, J=9Hz), 6.99 (1H, d, J=2Hz), 7.22 (1H, broad d, J=9Hz), 7.31 (1H, dd, J=2Hz, 9Hz), 7.39 (1H, t, J=8Hz), 7.79 (1H, t, J=1Hz), 7.98 (1H, dt, J=0.5Hz, 8Hz).
LC/MS t=3.77 min [MH+] 390.

b) 3-{2-[5-Trifluoromethyl-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Trifluoromethyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.085g, 0.219mmol), 4-chlorobenzyl bromide (0.068g, 0.329mmol) and potassium carbonate (0.061g, 0.438mmol) were heated in DMF (2ml) at 65°C in a nitrogen atmosphere for 3.5 hours. Upon cooling the mixture was diluted with EtOAc and washed with 2 x water. The organic layer was extracted and the aqueous layer washed with 3 x EtOAc. The combined organics were then washed with brine and concentrated *in vacuo*. The residue was purified by chromatography using a Biotage□ 25S column eluting with 8% EtOAc/iso-hexane. This yielded the title compound as a clear oil (0.078g, 69%).
^{1}H-NMR (400MHz, $CDCl_3$) 1.29 (3H, t, J=7Hz), 2.17 (3H, s), 4.28 (2H, q, J=7Hz), 4.77 (2H, s), 6.15 (1H, d, J=3Hz), 6.35 (1H, d, J=3Hz), 6.67 (1H, d, J=9Hz), 7.00 (2H, d, J=9Hz), 7.02 (1H, broad d, J=9Hz), 7.27-7.39 (4H, m), 7.50 (1H, d, J=2Hz), 7.70 (1H, t, J=1Hz), 7.91 (1H, dt, J=0.5Hz, 8Hz).
LC/MS t=4.33 min [MH^+] 514/516.

c) 3-{2-[5-Trifluoromethyl-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.



3-{2-[5-Trifluoromethyl-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.078g), 2M NaOH (1ml) and EtOH (2ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*, to yield the title compound as a brown solid (0.085g, 100%+pyrolidine equiv.)

^{1}H-NMR (400MHz, MeOD) 2.12 (3H, s), 4.89 (2H, s), 6.07 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.88 (1H, d, J=9Hz), 7.07 (1H, broad d, J=8Hz), 7.15 (2H, d, J=9Hz), 7.26-7.37 (5H, m), 7.72 (1H, broad s), 7.93 (1H, d, J=8Hz).

LC/MS t=4.09 min [MH^+] 486/488.

Example 75 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

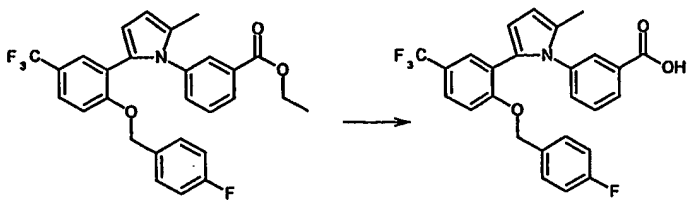
a) 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Trifluoromethyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.085g, 0.219mmol), 4-fluorobenzyl bromide (0.041g, 0.329mmol) and potassium carbonate (0.061g, 0.438mmol) were heated in DMF (2ml) at 65°C in a nitrogen atmosphere for 3.5 hours. Upon cooling the mixture was diluted with EtOAc and washed with 2 x water. The organic layer was extracted and the aqueous layer washed with 3 x EtOAc. The combined organics were then washed with brine and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with 8% EtOAc/iso-hexane. This yielded the title compound as a clear oil (0.088g, 81%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.30 (3H, t, J=7Hz), 2.16 (3H, s), 4.29 (2H, q, J=7Hz), 4.76 (2H, s), 6.15 (1H, d, J=3Hz), 6.35 (1H, d, J=3Hz), 6.69 (1H, d, J=9Hz), 6.97-7.13 (5H, m), 7.28 (1H, t, J=8Hz), 7.35 (1H, dd, J=2Hz,9Hz), 7.49 (1H, d, J=2Hz), 7.69 (1H, t, J=2Hz), 7.91 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t=4.21 min [MH^+] 498.

b) 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.088g), 2M NaOH (1ml) and EtOH (2ml) were heated at 100°C in a sealed

vessel for 45 minutes. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*, to yield the title compound as a brown solid (0.087g, 100% + pyrrolidine equivalent).

^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.79 (2H, s), 6.16 (1H, d, J=3Hz), 6.36 (1H, d, J=3Hz), 6.72 (1H, d, J=9Hz), 6.97-7.03 (2H, m), 7.06-7.10 (2H, m), 7.14-7.18 (1H, m), 7.32 (1H, t, J=8Hz), 7.36 (1H, dd, J=2Hz, 9Hz), 7.47 (1H, d, J=2Hz), 7.76 (1H, t, J=1Hz), 7.96 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t=3.95 min [MH^+] 470.

Example 76 3-{2-[5-Trifluoromethyl-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

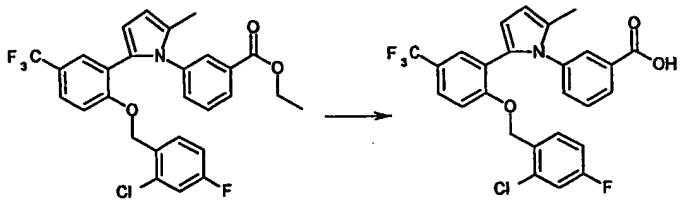
a) 3-{2-[5-Trifluoromethyl-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Trifluoromethyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.085g, 0.219mmol), 2-chloro-4-fluorobenzyl bromide (0.073g, 0.329mmol) and potassium carbonate (0.061g, 0.438mmol) were heated in DMF (2ml) at 65°C in a nitrogen atmosphere for 3.5 hours. Upon cooling the mixture was diluted with EtOAc and washed with 2 x water. The organic layer was extracted and the aqueous layer washed with 3 x EtOAc. The combined organics were then washed with brine and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with 8% EtOAc/iso-hexane. This yielded the title compound as a clear oil (0.091g, 78%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.29 (3H, t, J=7Hz), 2.18 (3H, s), 4.28 (2H, q, J=7Hz), 4.85 (2H, s), 6.17 (1H, d, J=3Hz), 6.37 (1H, d, J=3Hz), 6.67 (1H, d, J=9Hz), 6.86-6.97 (2H, m), 7.11 (1H, dd, J=2Hz, 9Hz), 7.15 (1H, broad d, J=9Hz), 7.31 (1H, t, J=8Hz), 7.37 (1H, dd, J=2Hz, 9Hz), 7.50 (1H, d, J=2Hz), 7.12 (1H, t, J=1Hz), 7.93 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t=4.34 min [MH^+] 532/534.

b) 3-{2-[5-Trifluoromethyl-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Trifluoromethyl-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.091g), 2M NaOH (1ml) and EtOH (2ml) were heated at 100°C in a sealed vessel for 45 minutes. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*, to yield the title compound as a brown solid (0.085g, 99%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.86 (2H, s), 6.17 (1H, d, J=3Hz), 6.37 (1H, d, J=3Hz), 6.71 (1H, d, J=9Hz), 6.92 (1H, ddd, J=2Hz, 8Hz), 6.98-7.04 (1H, m), 7.09 (1H, dd, J=2Hz, 8Hz), 7.20 (1H, broad d, J=8Hz), 7.33-7.39 (2H, m), 7.48 (1H, d, J=2Hz), 7.77 (1H, t, J=1Hz), 7.98 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t=4.10 min [MH^+] 504/506.

Example 77 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

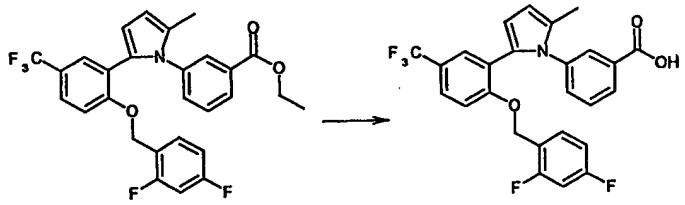
a) -{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Trifluoromethyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.085g, 0.219mmol), 2,4-difluorobenzyl bromide (0.043g, 0.329mmol) and potassium carbonate (0.061g, 0.438mmol) were heated in DMF (2ml) at 65°C in a nitrogen atmosphere for 3.5 hours. Upon cooling the mixture was diluted with EtOAc and washed with 2 x water. The organic layer was extracted and the aqueous layer washed with 3 x EtOAc. The combined organics were then washed with brine and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with 8% EtOAc/iso-hexane. This yielded the title compound as a clear oil (0.089g, 79%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7Hz), 2.18 (3H, s), 4.29 (2H, q, J=7Hz), 4.84 (2H, s), 6.14 (1H, d, J=3Hz), 6.34 (1H, d, J=3Hz), 6.74 (1H, d, J=9Hz), 6.77-6.83 (2H, m), 6.97-7.03 (1H, m) 7.13 (1H, broad d, J=8Hz), 7.30 (1H, t, J=8Hz), 7.37 (1H, dd, J=2Hz, 9Hz) 7.47 (1H, d, J=2Hz), 7.70 (1H, t, J=1Hz), 7.92 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t=4.22 min [MH^+] 516.

b) 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.089g), 2M NaOH (1ml) and EtOH (2ml) were heated at 100°C in a sealed vessel for 45 minutes. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*, to yield the title compound.

^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.85 (2H, s), 6.14 (1H, d, J=3Hz), 6.36 (1H, d, J=3Hz), 6.74-6.84 (3H, m), 7.03-7.08 (1H, m), 7.17-7.20 (1H, m) 7.33 (1H, t, J=8Hz), 7.38 (1H, dd, J=2Hz, 9Hz) 7.45 (1H, d, J=2Hz), 7.77 (1H, t, J=1Hz), 7.98 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t=3.97 min [MH^+] 488.

Example 78 3-{2-[5-Trifluoromethyl-2-(cyclohexylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

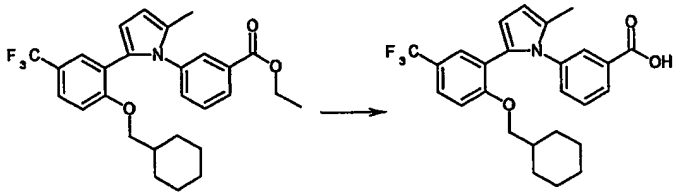
a) 3-{2-[5-Trifluoromethyl-2-(cyclohexylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl]-benzoic acid ethyl ester

3-{2-[5-Trifluoromethyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.085g, 0.219mmol), cyclohexylmethylene bromide (0.042ml, 0.329mmol) and potassium carbonate (0.061g, 0.438mmol) were heated in DMF (2ml) at 65°C in a nitrogen atmosphere for 3.5 hours. Upon cooling the mixture was diluted with EtOAc and washed with 2 x water. The organic layer was extracted and the aqueous layer washed with 3 x EtOAc. The combined organics were then washed with brine and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with 8% EtOAc/iso-hexane. This yielded the title compound as a clear oil (0.047g, 44%).

^{1}H-NMR (400MHz, $CDCl_3$) 0.80-0.96 (2H + excess, m), 1.10-1.31 (3H + excess, m), 1.36 (3H, t, J=7Hz), 1.65-1.73 (6H, m), 2.20 (3H, s), 3.51 (2H, d, J=7Hz), 4.34 (2H, q, J=7Hz), 6.13 (1H, d, J=3Hz), 6.34 (1H, d, J=3Hz), 6.73 (1H, d, J=9Hz), 7.18 (1H, d, J=9Hz), 7.30-7.37 (3H, m), 7.80 (1H, t, J=1Hz), 7.92 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t=4.50 min [MH^+] 486.

b) 3-{2-[5-Trifluoromethyl-2-(cyclohexylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Trifluoromethyl-2-(cyclohexylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.047g), 2M NaOH (1ml) and EtOH (2ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*, to yield the title compound.

^{1}H-NMR (400MHz, $CDCl_3$) 0.85-0.96 (2H + excess, m), 1.10-1.31 (3H + excess, m) 1.63-1.75 (6H, m), 2.20 (3H, s), 3.52 (2H, d, J=6Hz), 6.14 (1H, d, J=3Hz), 6.35 (1H, d, J=3Hz), 6.75 (1H, d, J=9Hz), 7.20-7.24 (1H, m), 7.30-7.39 (3H, m), 7.92 (1H, t, J=1Hz), 7.98 (1H, dt, J=0.5Hz, 8Hz).

LC/MS t=4.28 min [MH^+] 458.

Example 79 3-{2-[5-Trifluoromethyl-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 5-Trifluoromethyl-2-(4-methoxy-benzyloxy)-benzaldehyde

2-Hydroxy-5-trifluoromethyl-benzaldehyde (prepared *via* the procedure of *Schäfer, Synthesis* 2001, 15, 2259-2262) (0.25g, 1.32mmol), 4-methoxybenzyl chloride (0.269ml, 1.98mmol) and potassium carbonate (0.363g, 2.63mmol) were heated in DMF (7.5ml) at

60°C in a nitrogen atmosphere for 2 hour. Upon cooling the reaction mixture was diluted with EtOAc and washed with water. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were then washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. To yield the title compound as a yellow oil which was carried through without further purification.

^{1}H-NMR (400MHz, $CDCl_3$) 3.81 (3H, s) 5.19 (2H, s), 6.94 (2H, d, J=8Hz), 7.18 (1H, d, J=9Hz), 7.37 (2H, d, J=8Hz) 7.78 (1H, d, J=9Hz), 8.12 (1H, s) 10.55 (1H, s).

LC/MS t = 3.58 min.

b) 1-[5-Trifluoromethyl-2-(4-methoxy-benzyloxy)-phenyl]-pentane-1,4-dione

2-(4-Methoxy-benzyloxy)-5-trifluoromethyl-benzaldehyde (0.42g, 60%, 0.81mmol), triethylamine (0.337ml, 2.42mmol), methyl vinyl ketone (0.068ml, 0.82mmol) and 3-ethyl-5-(2-hydroxyethyl)-4-ethylthiazolium bromide (0.061g, 0.24mmol) were refluxed in EtOH (2ml) under a nitrogen atmosphere for 22 hours. Upon cooling the reaction mixture was diluted with EtOAc and washed with saturated NH_4Cl. The organic layer was extracted and the aqueous layer washed with 3 x EtOAc. The combined organic extracts were then washed with saturated $NaHCO_3$ and brine and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography, using Biotage□ 40M eluting with 15% EtOAc/iso-hexane. This yielded the title compound as an impure yellow oil (0.180g, 50% pure).

^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 2.77 (2H, t, J=6Hz), 3.22 (2H, t, J=6Hz), 3.73 (3H, s), 5.15 (2H, s), 6.91 (2H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.37 (2H, d, J=9Hz), 7.67 (1H, t, J=8Hz), 8.02 (1H, d, J=14Hz)

LC/MS t = 3.50 min.

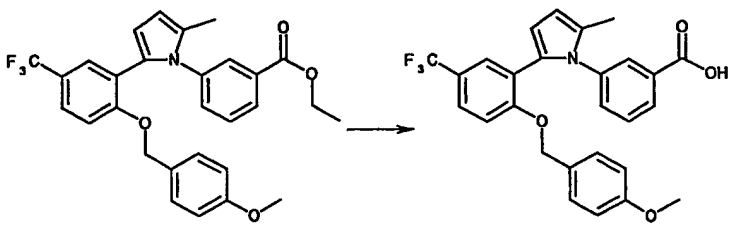
c) 3-{2-[5-Trifluoromethyl-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

1-[5-Trifluoromethyl-2-(4-methoxy-benzyloxy)-phenyl]-pentane-1,4-dione (0.180g, 50% pure, 0.24mmol) and ethyl-3-aminobenzoate (0.042ml, 0.28mmol) were heated in a sealed vessel at 140°C for 18 hours. Upon cooling the residue was purified by chromatography on silica gel eluting with 10% EtOAc/iso-hexane. This yielded the title compound as a yellow oil (0.03g, 25%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.29 (3H, t, J=7Hz), 2.15 (3H, s), 3.80 (3H, s) 4.28 (2H, q, J=7Hz), 4.74 (2H, s), 6.13 (1H, d, J=3Hz), 6.35 (1H, d, J=3Hz), 6.73 (1H, d, J=9Hz), 6.83 (2H, d, J=9Hz), 7.01 (2H, d, J=9Hz), 7.12 (1H, d, J=8Hz) 7.25-7.35 (2H, m), 7.46 (1H, d, J=2Hz), 7.70 (1H, s), 7.91 (1H, d, J=8Hz).

LC/MS t = 4.17 [MH^+] 510.

d) 3-{2-[5-Trifluoromethyl-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

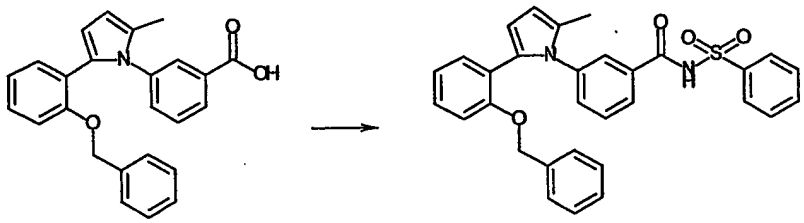


3-{2-[5-Trifluoromethyl-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.030g), 2M NaOH (1ml) and EtOH (2.5ml) were heated at 100°C in a sealed vessel for 30 minutes. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3 x EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*, to yield the title compound as a brown oil (0.019g, 67%)

^{1}H-NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 3.77 (3H, s), 4.75 (2H, s), 6.14 (1H, d, J=3Hz), 6.35 (1H, d, J=3Hz), 6.74 (1H, d, J=9Hz), 6.83 (2H, d, J=9Hz), 7.04 (2H, d, J=9Hz), 7.14-7.18 (1H, m) 7.28-7.36 (2H, m), 7.45 (1H, d, J=2Hz), 7.78 (1H, t, J=1Hz), 7.96 (1H, d, J=8Hz).

LC/MS t = 3.89 min [MH^-] 480.

Example 80 3-[2-(2-Benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-*N*-(1-phenylsulfonyl)-benzamide

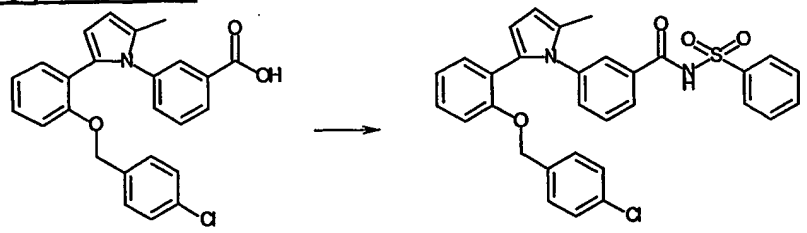


Benzenesulfonamide (31mg, 0.20mmol) was added to 3-[2-(2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-benzoic acid (40mg, 0.09mmol), carbonyl diimidazole (33mg, 0.20mmol) and diisopropylethylamine (0.035ml, 0.20mmol) in THF (2ml) and heated at reflux for 4 days. Upon cooling, the reaction mixture was diluted with EtOAc, washed with 2M HCl, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified using MDAP to give the title compound (10mg, 18%).

^{1}H-NMR (400MHz, d_6-DMSO) 2.05 (3H, s), 4.81 (2H, s), 6.04 (1H, d, J=3Hz), 6.17 (1H, d, J=3Hz), 6.77-6.84 (2H, m), 7.02-7.31 (8H, m), 7.38 (1H, t, J=8Hz), 7.55-7.73 (4H, m), 7.78 (1H, d, J=8Hz), 7.95 (2H, d, J=8Hz), 12.60 (1H, broad s).

LC/MS 1 t=4.15 min [MH^+] 423.

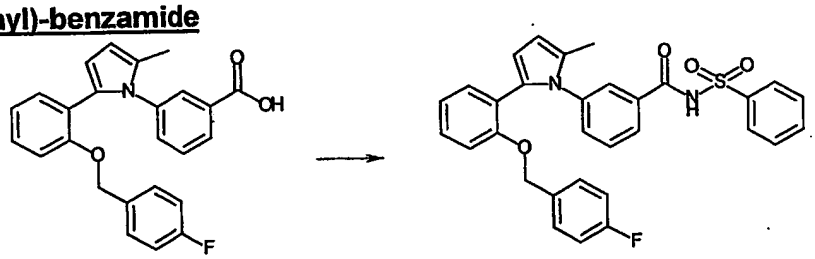
Example 81 3-{2-[2-(4-Chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenylsulfonyl)-benzamide



Benzenesulfonamide (31mg, 0.20mmol) was added to 3-{2-[2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (40mg, 0.09mmol), carbonyl diimidazole (33mg, 0.20mmol) and diisopropylethylamine (0.035ml, 0.20mmol) in THF (2ml) and heated at reflux for 4 days. Upon cooling, the reaction mixture was diluted with EtOAc, washed with

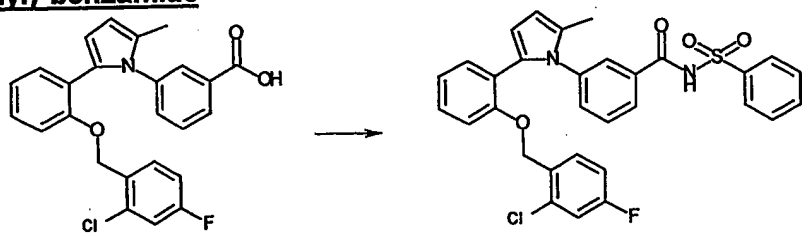
2M HCl, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified using MDAP to give the title compound (12mg, 24%).
^{1}H-NMR (400MHz, d_6-DMSO) 2.05 (3H, s), 4.81 (2H, s), 6.04 (1H, d, J=3.5Hz), 6.16 (1H, d, J=3.5Hz), 6.76-6.84 (2H, m), 7.03-7.16 (4H, m), 7.20 (1H, d, J=8Hz), 7.31-7.41 (3H, m), 7.55-7.73 (4H, m), 7.79 (1H, d, J=8Hz), 7.95 (2H, d, J=8Hz), 12.60 (1H, broad s).
LC/MS t=4.34 min [MH^+] 557/559.

Example 82 3-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenylsulfonyl)-benzamide



Benzenesulfonamide (31mg, 0.20mmol) was added to 3-{2-[2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (40mg, 0.10mmol), carbonyl diimidazole (33mg, 0.20mmol) and diisopropylethylamine (0.035ml, 0.20mmol) in dichloromethane (2ml) and heated at reflux for 2 days. Upon cooling, the reaction mixture was diluted with dichloromethane, washed with 2M HCl, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified using MDAP to give the title compound (19mg, 36%).
^{1}H-NMR (400MHz, d_6-DMSO) 1.99 (3H, s), 4.86 (2H, s), 5.99 (1H, d, J=3Hz), 6.13 (1H, d, J=3Hz), 6.76 (1H, t, J=8Hz), 6.85 (1H, d, J=9Hz), 6.95-6.99 (2H, m), 7.06-7.23 (4H, m), 7.26-7.39 (5H, m), 7.61 (1H, broad s), 7.76-7.82 (3H, m).
LC/MS t=4.18 min [MH^+] 541.

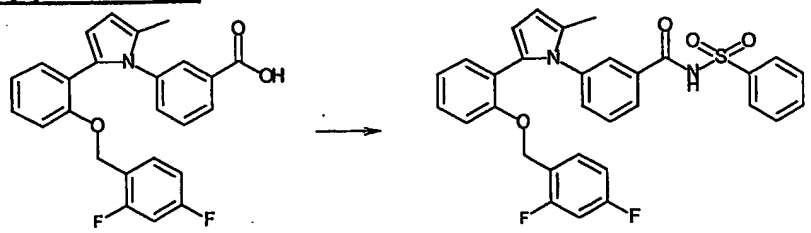
Example 83 3-{2-[2-(2-Chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenylsulfonyl)-benzamide



Benzenesulfonamide (31mg, 0.20mmol) was added to 3-{2-[2-(2-chloro-4-fluorobenzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (40mg, 0.09mmol), carbonyl diimidazole (33mg, 0.20mmol) and diisopropylethylamine (0.035ml, 0.20mmol) in THF (2ml) and heated at reflux for 4 days. Upon cooling, the reaction mixture was diluted with EtOAc, washed with 2M HCl, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified using MDAP to give the title compound (8mg, 15%).
^{1}H-NMR (400MHz, d_6-DMSO) 2.05 (3H, s), 4.82 (2H, s), 6.04 (1H, d, J=3.5Hz), 6.18 (1H, d, J=3.5Hz), 6.79-6.87 (2H, m), 7.04-7.16 (4H, m), 7.20 (1H, d, J=8Hz), 7.35-7.44 (2H, m), 7.54 (1H, broad s), 7.62 (2H, broad t, J=8Hz), 7.71 (1H, m), 7.79 (1H, d, J=8Hz), 7.95 (2H, d, J=8Hz), 12.55 (1H, broad s).

LC/MS t=4.37 min [MH^+] 575/577.

Example 84 3-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenylsulfonyl)-benzamide

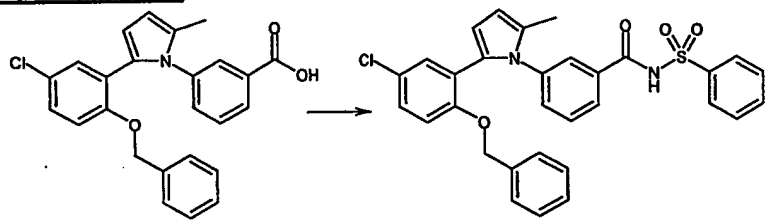


Benzenesulfonamide (31mg, 0.20mmol) was added to 3-{2-[2-(2,4-difluorobenzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (40mg, 0.09mmol), carbonyl diimidazole (33mg, 0.20mmol) and diisopropylethylamine (0.035ml, 0.20mmol) in THF (2ml) and heated at reflux for 4 days. Upon cooling, the reaction mixture was diluted with EtOAc, washed with 2M HCl, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified using MDAP to give the title compound (10mg, 20%).

^{1}H-NMR (400MHz, d_6-DMSO) 2.03 (3H, s), 4.81 (2H, s), 6.02 (1H, d, J=3.5Hz), 6.14 (1H, d, J=3.5Hz), 6.82 (1H, t, J=8Hz), 6.89 (1H, d, J=8Hz), 6.96-7.05 (2H, m), 7.10-7.22 (4H, m), 7.37 (1H, t, J=8Hz), 7.52 (1H, broad s), 7.58-7.72 (3H, m), 7.79 (1H, d, J=8Hz), 7.95 (2H, d, J=8Hz), 12.60 (1H, broad s).

LC/MS t=4.19 min [MH^+] 559.

Example 85 3-[2-(5-Chloro-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-*N*-(1-phenylsulfonyl)-benzamide

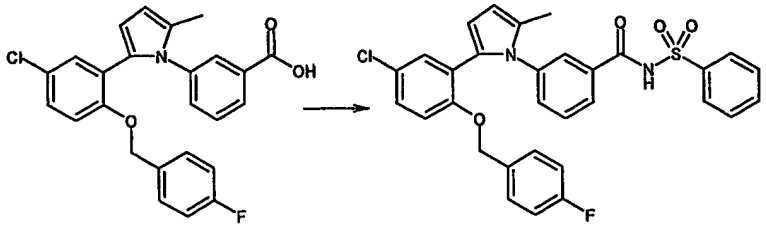


3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (0.02g, 0.048mmol), carbonyldiimidazole (0.016g, 0.096mmol), diisopropylethylamine (0.017ml, 0.096mmol), benzenesulfonamide (0.015g, 0.096mmol) and DCM (4ml) were stirred under a nitrogen atmosphere at reflux for 5 days. The reaction was diluted with DCM and washed with 2M HCl. The organics were separated and the aqueous washed with 3x DCM, the combined organics were then dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to yield a white solid which was purified on mass-directed auto prep to yield the title compound as a white solid (0.012g, 44%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.11 (3H, s), 4.71 (2H, s), 6.13 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.62 (1H, d, J=9Hz), 7.02-7.05 (2H, m), 7.08 (1H, dd, J=3Hz, 9Hz), 7.15 (1H, d, J=9Hz), 7.20 (1H, d, J=3Hz), 7.27-7.31 (5H, m), 7.52-7.67 (4H, m), 8.09 (2H, d, J=8Hz).

LC/MS t=4.35 min [MH^+] 557.

Example 86 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenylsulfonyl)-benzamide

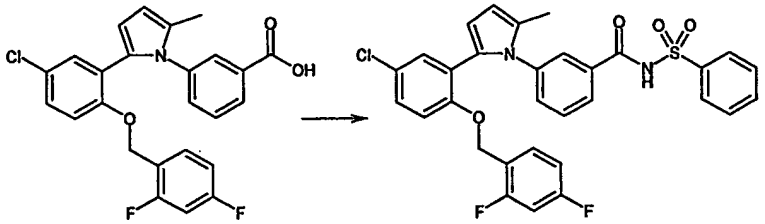


3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (0.02g, 0.046mmol), carbonyldiimidazole (0.015g, 0.092mmol), diisopropylethylamine (0.016ml, 0.092mmol), benzenesulfonamide (0.014g, 0.092mmol) and DCM (4ml) were stirred under a nitrogen atmosphere at reflux for 5 days. The reaction was diluted with DCM and washed with 2M HCl. The organics were separated and the aqueous washed with 3x DCM, the combined organics were then dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to yield a white solid which was purified on mass-directed auto prep to yield the title compound as a white solid (0.011g, 42%)

^{1}H-NMR (400MHz, $CDCl_3$) 2.10 (3H, s), 4.69 (2H, s), 6.12 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.61 (1H, d, J=9Hz), 6.94-6.99 (2H, m), 7.02-7.05 (2H, m), 7.07 (1H, dd, J=3Hz, 9Hz), 7.15-7.17 (1H, m), 7.18 (1H, d, J=3Hz), 7.30 (1H, t, J=8Hz), 7.37 (1H, broad s), 7.53-7.68 (4H, m), 8.10 (2H, d, J=8Hz).

LC/MS t=4.36 min [MH^+] 575.

Example 87 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenylsulfonyl)-benzamide

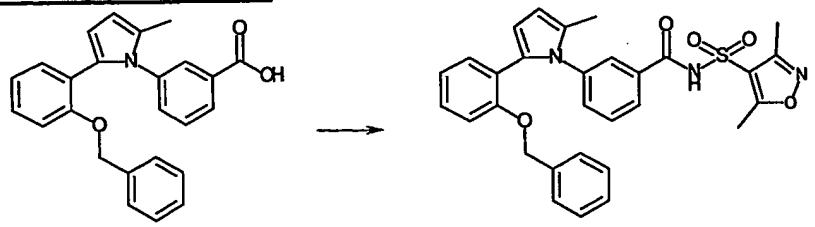


3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (0.03g, 0.066mmol), carbonyldiimidazole (0.012g, 0.073mmol), diisopropylethylamine (0.013ml, 0.073mmol), benzenesulfonamide (0.012g, 0.073mmol) and DCM (5ml) were stirred under a nitrogen atmosphere at reflux for 2 days. The reaction was diluted with DCM and washed with 2M HCl. The organics were separated and the aqueous washed with 3x DCM, the combined organics were then dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to yield a white solid which was purified on mass-directed auto prep to yield the title compound as a white solid (0.019g, 49%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.09 (3H, s), 4.70 (2H, s), 6.08 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.62 (1H, d, J=9Hz), 6.68-6.79 (2H, m), 6.95-7.02 (1H, m), 7.16 (1H, dd, J=3Hz, 9Hz), 7.12-7.17 (2H, m), 7.25-7.31 (1H + excess, m), 7.46 (1H, broad s), 7.52-7.57 (2H, m), 7.63-7.68 (2H, m), 8.10 (2H, d, J=8Hz).

LC/MS t=4.40 min [MH+] 593/595.

Example 88 3-[2-(2-Benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-*N*-(3,5-dimethyl-isoxazole-4-sulfonyl)-benzamide

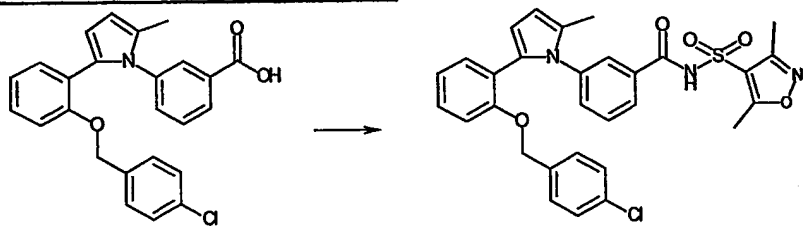


3,5-Dimethyl-isoxazole-4-sulfonamide (35mg, 0.20mmol) was added to 3-{-[2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (40mg, 0.09mmol), carbonyl diimidazole (33mg, 0.20mmol) and diisopropylethylamine (0.035ml, 0.20mmol) in THF (2ml) and heated at reflux for 4 days. Upon cooling, the reaction mixture was diluted with EtOAc, washed with 2M HCl, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified using MDAP to give the title compound (16mg, 30%).

^{1}H-NMR (400MHz, d_6-DMSO) 2.06 (3H, s), 2.31 (3H, s), 2.63 (3H, s), 4.85 (2H, s), 6.04 (1H, d, J=3Hz), 6.18 (1H, d, J=3Hz), 6.76-6.84 (2H, m), 7.01-7.34 (8H, m), 7.38 (1H, t, J=8Hz), 7.62 (1H, broad s), 7.81 (1H, d, J=8Hz), 12.90 (1H, broad s).

LC/MS t=4.31 min [MH^+] 542.

Example 89 3-{2-[2-(4-Chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(3,5-dimethyl-isoxazole-4-sulfonyl)-benzamide

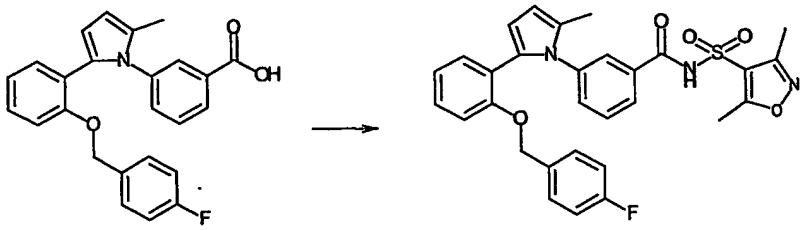


3,5-Dimethyl-isoxazole-4-sulfonamide (35mg, 0.20mmol) was added to 3-{2-[2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (40mg, 0.09mmol), carbonyl diimidazole (33mg, 0.20mmol) and diisopropylethylamine (0.035ml, 0.20mmol) in THF (2ml) and heated at 75°C for 4 days. Upon cooling, the reaction mixture was diluted with EtOAc, washed with 2M HCl, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified using MDAP to give the title compound (10mg, 19%).

^{1}H-NMR (400MHz, d_6-DMSO) F7465 2.06 (3H, s), 2.30 (3H, s), 2.63 (3H, s), 4.84 (2H, s), 6.04 (1H, d, J=3.5Hz), 6.17 (1H, d, J=3.5Hz), 6.56 (1H, broad s), 6.82 (2H, t, J=8Hz), 7.03-7.23 (5H, m), 7.32-7.41 (3H, m), 7.60 (1H, broad s), 7.82 (1H, d, J=8Hz).

LC/MS CF107228-1 t=4.50 [MH^+] 576/578.

Example 90 3-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(3,5-dimethyl-isoxazole-4-sulfonyl)-benzamide

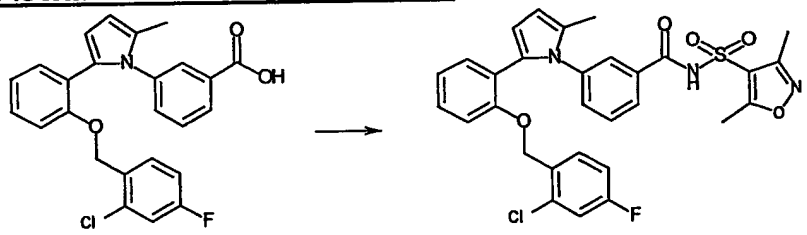


3,5-Dimethyl-isoxazole-4-sulfonamide (35mg, 0.20mmol) was added to 3-{2-[2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (40mg, 0.10mmol), carbonyl diimidazole (33mg, 0.20mmol) and diisopropylethylamine (0.035ml, 0.20mmol) in dichloromethane (2ml) and heated at reflux for 2 days. Upon cooling, the reaction mixture was diluted with dichloromethane, washed with 2M HCl, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified using MDAP to give the title compound (12mg, 21%).

^{1}H-NMR (400MHz, d_6-DMSO) 2.05 (3H, s), 2.30 (3H, s), 2.62 (3H, s), 4.83 (2H, s), 6.03 (1H, d, J=3.5Hz), 6.16 (1H, d, J=3.5Hz), 6.53 (1H, broad s), 6.77-6.85 (2H, m), 7.04 (1H, d, J=7.5Hz), 7.07-7.25 (6H, m), 7.32-7.41 (1H, m), 7.60 (1H, broad s), 7.81 (1H, d, J=8Hz).

LC/MS t=4.34 min [MH^+] 560.

Example 91 3-{2-[2-(2-Chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(3,5-dimethyl-isoxazole-4-sulfonyl)-benzamide

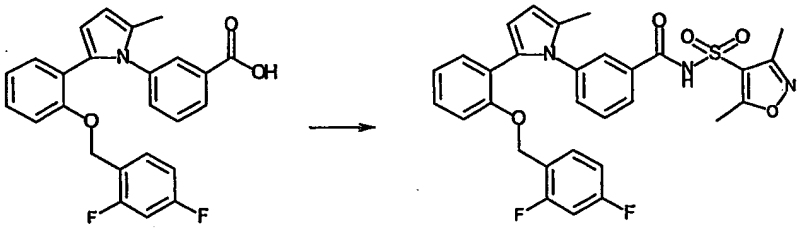


3,5-Dimethyl-isoxazole-4-sulfonamide (35mg, 0.20mmol) was added to 3-{2-[2-(2-chloro-4-fluorobenzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (40mg, 0.09mmol), carbonyl diimidazole (33mg, 0.20mmol) and diisopropylethylamine (0.035ml, 0.20mmol) in THF (2ml) and heated at reflux for 4 days. Upon cooling, the reaction mixture was diluted with EtOAc, washed with 2M HCl, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified using MDAP to give the title compound (7mg, 13%).

^{1}H-NMR (400MHz, d_6-DMSO) 2.06 (3H, s), 2.30 (3H, s), 2.62 (3H, s), 4.83 (2H, s), 6.04 (1H, d, J=3.5Hz), 6.19 (1H, d, J=3.5Hz), 6.82 (1H, t, J=8Hz), 6.90 (1H, d, J=8Hz), 6.99-7.06 (2H, m), 7.10-7.25 (4H, m), 7.33-7.40 (1H, m), 7.56 (1H, broad s), 7.81 (1H, d, J=8Hz), 12.80 (1H, broad s).

LC/MS t=4.55 min [MH^+] 594/596.

Example 92 3-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(3,5-dimethyl-isoxazole-4-sulfonyl)-benzamide



3,5-Dimethyl-isoxazole-4-sulfonamide (35mg, 0.20mmol) was added to 3-{2-[2-(2,4-difluorobenzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (40mg, 0.09mmol), carbonyl diimidazole (33mg, 0.20mmol) and diisopropylethylamine (0.035ml, 0.20mmol) in THF (2ml) and heated at reflux for 4 days. Upon cooling, the reaction mixture was diluted with EtOAc, washed with 2M HCl, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified using MDAP to give the title compound (12mg, 23%).
^{1}H-NMR (400MHz, d_6-DMSO) 2.04 (3H, s), 2.32 (3H, s), 2.63 (3H, s), 4.84 (2H, s), 6.02 (1H, d, J=3.5Hz), 6.15 (1H, d, J=3.5Hz), 6.52 (1H, broad s), 6.81-6.87 (2H, m), 7.04-7.22 (5H, m), 7.33-7.44 (2H, m), 7.57 (1H, broad s), 7.82 (1H, d, J=8Hz).
LC/MS t=4.37 min [MH^+] 578.

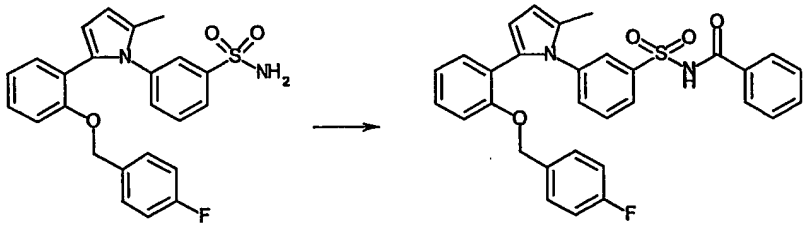
Example 93 3-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenyl-methanoyl)-benzenesulfonamide

a) 2-(4-Fluoro-benzyloxy)-benzaldehyde
Procedure as for 2-benzyloxy-5-chloro-benzaldehyde to give the title compound.
LCMS t=3.30 min

b) 1-[2-(4-Fluoro-benzyloxy)-phenyl]-pentane-1,4-dione
Procedure as for 1-[5-chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione to give the title compound.
LCMS t=3.29 min.

c) 3-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzene-sulfonamide
1-[2-(4-Fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (1.5g, 5mmol), 3-aminobenzenesulfonamide (1.03g, 6mmol) (ex. Maybridge), *para*-toluenesulfonic acid (0.19g, 1mmol) and toluene (30ml) were stirred at reflux in a nitrogen atmosphere for 19 hours. The solvent was removed in *vacuo* and the residue taken up in EtOAc and the solution washed with $NaHCO_3$. The organics were extracted and the aqueous washed with 2 x EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by chromatography using Biotage□ 40M was purified by chromatography on silica gel eluting with a gradient of 15%-30% EtOAc/*iso*-hexane. This yielded the title compound as a pale yellow solid (1.53g, 70%).
^{1}H-NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 4.34 (2H, broad s), 4.72 (2H, s), 6.15 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.65 (1H, d, J=8Hz), 6.92 (1H, t, J=7Hz), 6.97-7.08 (4H, m), 7.11-7.18 (2H, m), 7.27 (1H, m), 7.34 (1H, t, J=7Hz), 7.49 (1H, t, J=1Hz), 7.72 (1H, m).
LC/MS t=3.62 min [MH^+] 437.

d) 3-{2-[2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenyl-methanoyl)-benzenesulfonamide



Benzoyl chloride (0.030ml, 0.25mmol) was added to 3-{2-[2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzenesulfonamide (93mg, 0.21mmol), DMAP (26mg, 0.21mmol) and triethylamine (0.035ml, 0.25mmol) in dichloromethane (1ml) and stirred at room temperature for 16 hours. The reaction mixture was diluted with dichloromethane, washed with 2M aqueous citric acid, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (15-25%) as eluant, to give the title compound (116mg, 100%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 4.59 (2H, s), 6.18 (1H, d, J=3.5Hz), 6.28 (1H, d, J=3.5Hz), 6.35 (1H, d, J=8Hz), 6.69 (1H, ddd, J=2, 9Hz), 6.76 (1H, broad t, J=8Hz), 6.92-7.02 (4H, m), 7.18-7.23 (2H, m), 7.37 (1H, t, J=8Hz), 7.48 (2H, t, J=8Hz), 7.57-7.69 (4H, m), 8.04 (1H, broad d, J=8Hz), 8.50 (1H, broad s).

LC/MS t=4.11 min [MH^+] 541.

Example 94 3-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenyl-methanoyl)-benzenesulfonamide

a) 2-(2,4-Difluoro-benzyloxy)-benzaldehyde

Procedure as for 2-benzyloxy-5-chloro-benzaldehyde to give the title compound.

LCMS t=3.36 min

b) 1-[2-(2,4-Difluoro-benzyloxy)-phenyl]-pentane-1,4-dione

Procedure as for 1-[5-chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione to give the title compound.

LCMS t=3.32 min

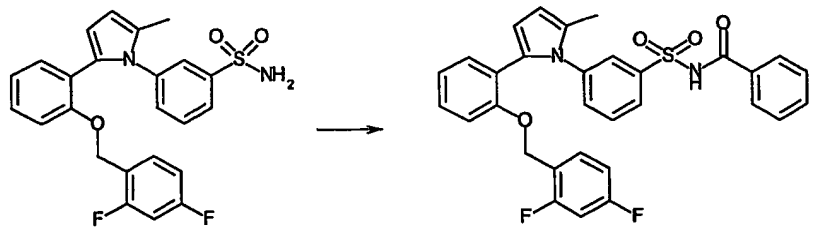
c) 3-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzene-sulfonamide

1-[2-(2,4-Difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (1g, 2.20mmol), 3-aminonobenzenesulfonamide (0.65g, 2.64mmol), *para*-toluenesulfonic acid (cat.) and toluene (50ml) were stirred at reflux in a nitrogen atmosphere for 34 hours. The solvent was removed in *vacuo* and the residue taken up in EtOAc and the solution washed with 2N HCl and $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by chromatography on silica gel eluting with a gradient of 20% EtOAc/*iso*-hexane. This yielded the title compound as a pale yellow solid (1.75g, 100%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 4.61 (2H, broad s), 4.77 (2H, s), 6.12 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.69 (1H, d, J=8Hz), 6.75-6.84 (2H, m), 6.91 (1H, t, J=7Hz), 6.99-7.06 (1H, m), 7.12-7.25 (3H, m), 7.34 (1H, t, J=7Hz), 7.51 (1H, t, J=1Hz), 7.72 (1H, m).

LC/MS t=3.62 min [MH^+] 455.

d) 3-{2-[2-(2,4-Difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenyl-methanoyl)-benzenesulfonamide



Benzoyl chloride (0.030ml, 0.25mmol) was added to 3-{2-[2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzenesulfonamide (97mg, 0.21mmol), DMAP (26mg, 0.21mmol) and triethylamine (0.035ml, 0.25mmol) in dichloromethane (1ml) and stirred at room temperature for 16 hours. The reaction mixture was diluted with dichloromethane, washed with 2M aqueous citric acid, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (15-25%) as eluant, to give the title compound (99mg, 81%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.21 (3H, s), 4.70 (2H, s), 6.14 (1H, d, J=3.5Hz), 6.27 (1H, d, J=3.5Hz), 6.39-6.45 (1H, m), 6.69-6.82 (4H, m), 6.89-6.96 (1H, m), 7.15-7.20 (1H, m), 7.24-7.28 (1H, m), 7.41 (2H, t, J=8Hz), 7.47 (1H, t, J=8Hz), 7.61 (1H, broad t, J=8Hz), 7.68 (2H, broad d, J=8Hz), 7.74 (1H, t, J=1.5Hz), 8.04 (1H, broad d, J=8Hz), 8.50 (1H, broad s).

LC/MS t=4.13 min [MH^+] 559.

<u>Example 95 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenyl-methanoyl)-benzenesulfonamide</u>

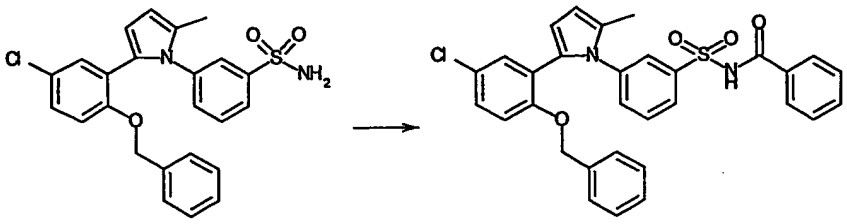
a) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzene-sulfonamide

1-[5-chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione (1g, 3.2mmol), 3-amino-benzenesulfonamide (654mg, 3.8mmol) and *para*-toluenesulfonic acid (120mg, 0.63mmmol) were heated at 110°C in toluene (32ml) for 16 hours. Upon cooling, the mixture was concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (25%) as eluant, to give the title compound (1.52g, 100%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.19 (3H, s), 4.25 (2H, s), 4.75 (2H, s), 6.16 (1H, d, J=3.5Hz), 6.33 (1H, d, J=9Hz), 6.58 (1H, d, J=9Hz), 7.01 (2H, broad d, J=8Hz), 7.08 (1H, dd, J=3, 9Hz), 7.13 (1H, broad d, J=8Hz), 7.25-7.43 (5H, m), 7.57 (1H, broad s), 7.74 (1H, broad d, J=8Hz).

LC/MS t=3.73 min [MH^+] 453/455.

b) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenyl-methanoyl)-benzenesulfonamide

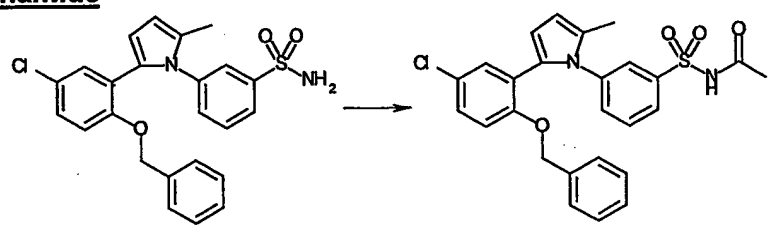


Benzoyl chloride (0.030ml, 0.25mmol) was added to 3-[2-(5-chloro-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-benzenesulfonamide (96mg, 0.21mmol), DMAP (26mg, 0.21mmol) and triethylamine (0.035ml, 0.25mmol) in dichloromethane (1ml) and stirred at room temperature for 16 hours. The reaction mixture was diluted with dichloromethane, washed with 2M aqueous citric acid, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (15-25%) as eluant, to give the title compound (95mg, 80%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 4.60 (2H, s), 6.14 (1H, d, J=3.5Hz), 6.25 (1H, d, J=9Hz), 6.29 (1H, d, J=3.5Hz), 6.53 (1H, dd, J=3, 9Hz), 6.97 (2H, broad d, J=8Hz), 7.18-7.31 (5H, m), 7.39 (1H, t, J=8Hz), 7.47 (1H, broad t, J=8Hz), 7.58-7.67 (3H, m), 7.70 (1H, broad t, J=1.5Hz), 8.07 (1H, broad d, J=8Hz), 8.44 (1H, broad s).

LC/MS t=4.27 min [MH^+] 557/559.

Example 96 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-acetyl-benzenesulfonamide

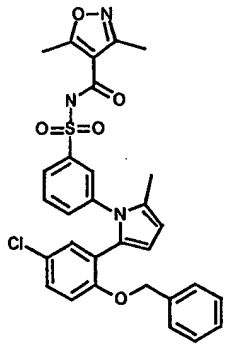


3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzenesulfonamide (0.20g, 0.442mmol), acetic anhydride (0.046ml, 0.486mmol), pyridine (0.072ml, 0.884mmol), dimethylaminopyridine (cat.) and DCM (2.5ml) were stirred at reflux for 30 minutes. The reaction was washed with 2M HCl and the solvent removed *in vacuo* to yield the title compound as a brown oil (0.240g).

^{1}H-NMR (400MHz, $CDCl_3$) 1.89 (3H, s), 2.12 (3H, s), 4.72 (2H, s), 6.16 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.54 (1H, d, J=9Hz), 7.00-7.05 (3H, m), 7.18-7.22 (2H, m), 7.27-7.32 (2H, m), 7.35-7.42 (2H, m), 7.69 (1H, broad s), 7.92 (1H, d, J=8Hz).

LC/MS t=3.78 min [MH^+] 495/497.

Example 97: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-[1-(3,5-dimethyl-isoxazol-4-yl)-methanoyl]-benzenesulfonamide

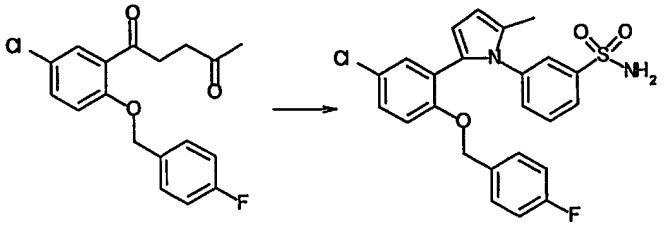


Prepared in the same way as 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-[1-phenyl-methanoyl]-benzenesulfonamide.

LC/MS t=4.51 min, [MH$^+$] 576, 578; [MH$^-$] 574, 576.

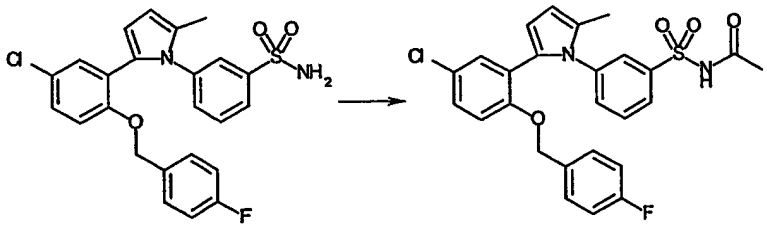
Example 98 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-acetyl-benzenesulfonamide

a) 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzenesulfonamide



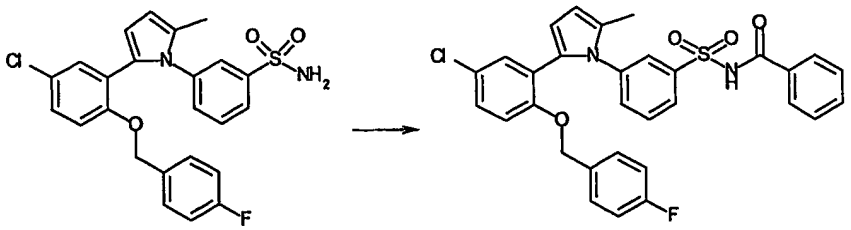
1-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (750mg, 2.25mmol), 3-amino-benzenesulfonamide (464mg, 2.69mmol) and *para*-toluenesulfonic acid (85mg, 0.45mmol) were heated at reflux in toluene (22ml) for 16 hours. Upon cooling, the mixture was concentrated *in vacuo*. The residue w was purified by chromatography on silica gel with isohexane / EtOAc (25%) as eluant, to give the title compound (631mg, 60%).
^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.53 (2H, s), 4.71 (2H, s), 6.14 (1H, dd, J=1Hz, 3Hz), 6.32 (1H, d, J=3Hz), 6.57 (1H, d, J=9Hz), 6.97-7.09 (5H, m), 7.13-7.17 (1H, m), 7.21 (1H, d, J=2.5Hz), 7.37 (1H, t, J=8Hz), 7.51 (1H, t, J=0.5Hz), 7.74-7.79 (1H, m).
LC/MS t=3.75 min [MH$^+$] = 471/473.

b) 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-acetyl-benzenesulfonamide



3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzenesulfonamide (0.20g, 0.426mmol), acetic anhydride (0.044ml, 0.469mmol), pyridine (0.069ml, 0.852mmol), dimethylaminopyridine (cat.) and DCM (2.5ml) were stirred at reflux for 30 minutes. The reaction was washed with 2M HCl and the solvent removed in vacuo to yield the title compound as a brown oil (0.249g).
^{1}H-NMR (400MHz, $CDCl_3$) 1.92 (3H, s), 2.18 (3H, s), 4.68 (2H, s), 6.16 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.53 (1H, d, J=9Hz), 6.96-7.02 (4H, m), 7.05 (1H, dd, J=3Hz, 9Hz), 7.16-7.19 (1H, m), 7.22 (1H, d, J=3Hz), 7.37 (1H, t, J=8Hz), 7.67 (1H, broad s), 7.92 (1H, d, J=8Hz).
LC/MS t=3.80 min [MH$^+$] 513/515.

Example 99 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenyl-methanoyl)-benzenesulfonamide



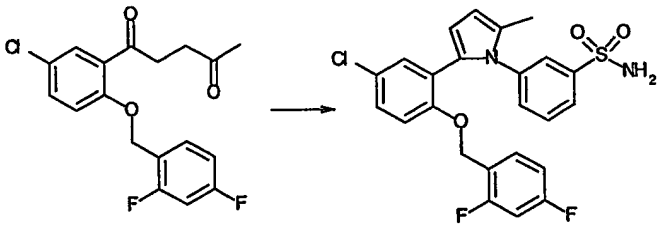
Benzoyl chloride (0.075ml, 0.63mmol) was added to 3-{2-[5-chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzenesulfonamide (100mg, 0.21mmol), DMAP (26mg, 0.21mmol) and triethylamine (0.060ml, 0.42mmol) in dichloromethane (1ml) and stirred at room temperature for 16 hours. The reaction mixture was diluted with dichloromethane, washed with 2M citric acid, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (25%) as eluant, to give the title compound (57mg, 47%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.56 (2H, s), 6.13 (1H, d, J=3.5Hz), 6.28 (2H, d, J=3.5Hz), 6.58 (1H, dd, J=2.5, 9Hz), 6.93-6.98 (4H, m), 7.19 (1H, broad d, J=8Hz), 7.22 (1H, d, J=3Hz), 7.39 (1H, t, J=8Hz), 7.48 (2H, broad t, J=8Hz), 7.58-7.72 (4H, m), 8.06 (1H, broad d, J=8Hz), 8.57 (1H, broad s).

LC/MS t=4.28 min [MH^+] 575/577.

Example 100 3-{2-[5-chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-acetyl-benzenesulfonamide

a) 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzenesulfonamide

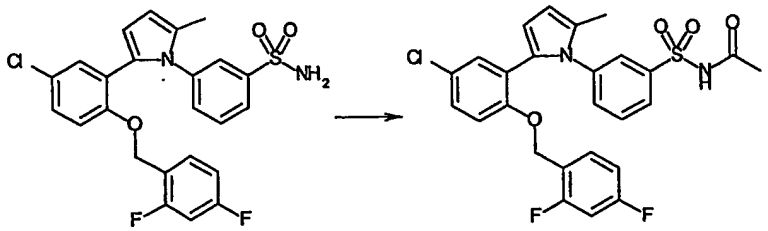


1-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (1.5g, 4.0mmol), 3-amino-benzenesulfonamide (881mg, 5.0mmol) and *para*-toluenesulfonic acid (162mg, 0.85mmol) were heated at 110°C in toluene (43ml) for 16 hours. Upon cooling, the mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel with isohexane / EtOAc (30%) as eluant, to give the title compound (1.53g, 74%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.60 (2H, s), 4.76 (2H, s), 6.14 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.62 (1H, d, J=9Hz), 6.77-6.87 (2H, m), 6.96-7.05 (1H, m), 7.09 (1H, dd, J=2.5Hz, 9Hz), 7.15-7.20 (2H, m), 7.39 (1H, t, J=8Hz), 7.57 (1H, t, J=0.5Hz), 7.78 (1H, dt, J=0.5Hz, 8Hz).

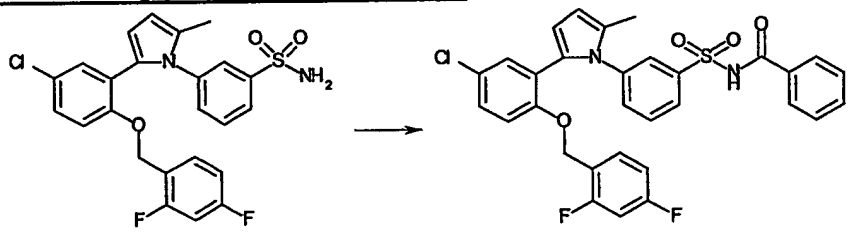
LC/MS t=3.76 min [MH^+] = 489/491.

b) 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-acetyl-benzenesulfonamide



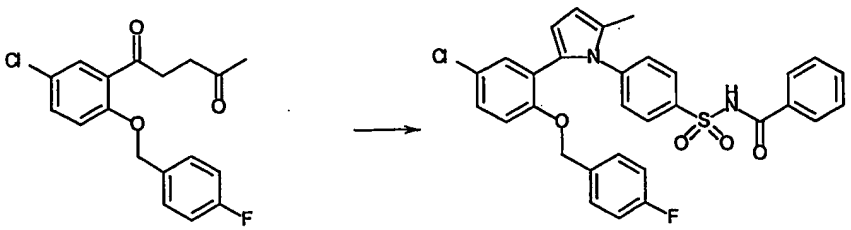
3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzenesulfonamide (0.20g, 0.410mmol), acetic anhydride (0.043ml, 0.485mmol), pyridine (0.066ml, 0.820mmol), dimethylaminopyridine (cat.) and DCM (2.5ml) were stirred at reflux for 30 minutes. The reaction was washed with 2M HCl and the solvent removed in vacuo to yield the title compound as a brown oil (0.249g).
^{1}H-NMR (400MHz, $CDCl_3$) 1.97 (3H, s), 2.18 (3H, s), 4.75 (2H, s), 6.14 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.60 (1H, d, J=9Hz), 6.77-6.84 (2H, m), 6.92-7.00 (1H, m), 7.08 (1H, dd, J=3Hz, 9Hz), 7.18 (1H, d, J=3Hz), 7.22-7.25 (1H, m), 7.42 (1H, t, J=8Hz), 7.71 (1H, broad s), 7.92 (1H, d, J=8Hz).
LC/MS t=3.82 min [MH^+] 531/533.

Example 101 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenyl-methanoyl)-benzenesulfonamide



Benzoyl chloride (0.030ml, 0.25mmol) was added to 3-{2-[5-chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzenesulfonamide (104mg, 0.21mmol), DMAP (26mg, 0.21mmol) and triethylamine (0.035ml, 0.25mmol) in dichloromethane (1ml) and stirred at room temperature for 16 hours. The reaction mixture was diluted with dichloromethane, washed with 2M citric acid, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (15-25%) as eluant, to give the title compound (102mg, 81%).
^{1}H-NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 4.67 (2H, s), 6.13 (1H, d, J=3.5Hz), 6.27 (1H, d, J=3.5Hz), 6.34 (1H, d, J=9Hz), 6.66 (1H, dd, J=3, 9Hz), 6.69-6.90 (3H, m), 7.19 (1H, d, J=2.5Hz), 7.24 (1H, broad s), 7.40-7.51 (3H, m), 7.59-7.65 (1H, m), 7.69 (2H, broad d, J=8Hz), 7.78 (1H, broad s), 8.06 (1H, broad d, J=8Hz), 8.60 (1H, broad s).
LC/MS t=4.31 min [MH^+] 593/595.

Example 102 4-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenyl-methanoyl)-benzenesulfonamide

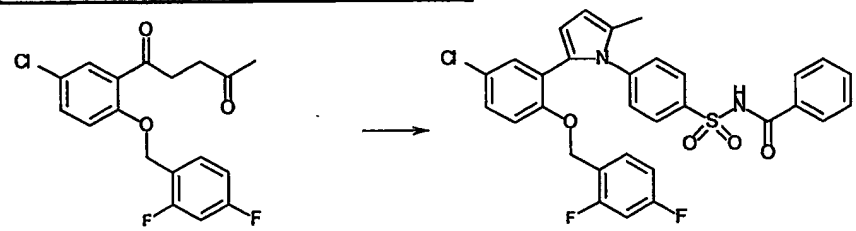


1-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (100mg, 0.30mmol), 4-amino-*N*-(1-phenyl-methanoyl)-benzenesulfonamide (0.99mg, 0.36mmol) and *para*-toluenesulfonic acid (11mg, 0.06mmmol) were heated at reflux in toluene (3ml) for 2 hours. Upon cooling, the mixture was concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (35%) as eluant, to give the title compound (87mg, 51%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 4.50 (2H, s), 6.13 (1H, broad d, J=3Hz), 6.29 (1H, dd, J=1, 3Hz), 6.50 (1H, d, J=9Hz), 6.96-7.09 (8H, m), 7.47 (2H, broad t, J=8Hz), 7.61 (1H, broad t, J=8Hz), 7.78 (2H, broad d, J=8Hz), 7.95 (2H, broad d, J=8Hz).

LC/MS t=4.29 min [MH^+] 575/577.

Example 103 4-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-phenyl-methanoyl)-benzenesulfonamide

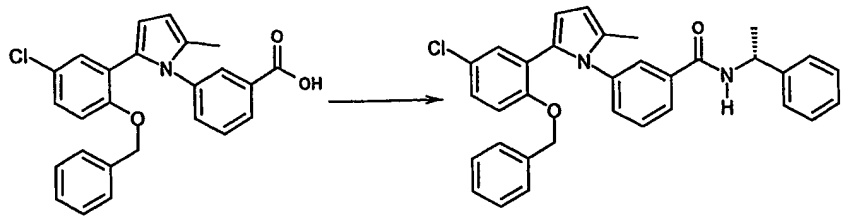


1-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (103mg, 0.30mmol), 4-amino-*N*-(1-phenyl-methanoyl)-benzenesulfonamide (99mg, 0.36mmol) and *para*-toluenesulfonic acid (11mg, 0.06mmmol) were heated at reflux in toluene (3ml) for 2 hours. Upon cooling, the mixture was concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (35%) as eluant, to give the title compound (126mg, 71%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.62 (2H, s), 6.12 (1H, d, J=3.5Hz), 6.29 (1H, d, J=3.5Hz), 6.56 (1H, d, J=9Hz), 6.75-6.88 (2H, m), 6.95-7.10 (4H, m), 7.21 (1H, d, J=3Hz), 7.45 (2H, broad t, J=8Hz), 7.59 (1H, broad t, J=8Hz), 7.77 (2H, broad d, J=8Hz), 8.00 (2H, d, J=8Hz), 8.88 (1H, broad s).

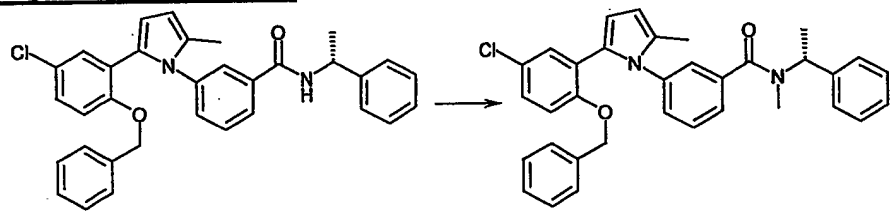
LC/MS t=4.26 min [MH^+] 593/595.

Example 104 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-[(*R*)-1-phenyl-ethyl]-benzamide



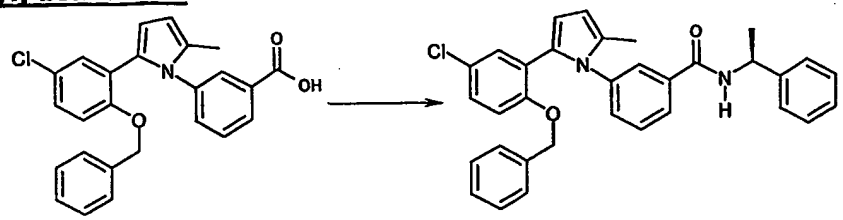
3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-benzoic acid (0.12g, 0.575mmol, 1eq) was dissolved in DCM (2.5ml), EDAC (0.0715g, 0.747mmol, 1.3eq) and HOBt (0.0505g, 0.747mmol, 1.3eq) were added to the reaction vessel and stirred for 5min at 21°C. (*R*)-Phenylethylamine (0.139g, 0.115mmol, 2eq) was then added and stirred for 6 hours at room temperature The reaction mixture was then diluted with ethyl acetate and washed with saturated NH_4Cl and saturated $NaHCO_3$. The combined organic extracts were washed with brine and dried ($MgSO_4$), filtered and volatiles removed *in vacuo* to yield title compound (0.107g, 0.206mmol, 36%) as a clear yellow oil.
LC/MS t=4.10 min [MH+] 521/523.

Example 105 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-methyl-*N*-[(*R*)-1-phenyl-ethyl]-benzamide



3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-[(*R*)-1-phenyl-ethyl]-benzamide (0.050g, 0.096mmol, 1eq), was dissolved in DMF (1ml) and sodium hydride (6mg, 0.24mmol, 1.5eq) was added at 0°C and stirred for 1 hour. Methyliodide (0.0065ml, 0.021mmol, 1.1eq) was then added and the reaction allowed to warm to room temperature with stirring for 2 hours. The volatiles were removed *in vacuo* the reaction mixture was diluted with EtOAc, and washed with water. The combined organic extracts were washed with brine and dried ($MgSO_4$), filtered and volatiles removed *in vacuo* to yield the title compound (0.021g, 82%) as a yellow solid.
LC/MS t=4.13 min [MH+] 535/537.

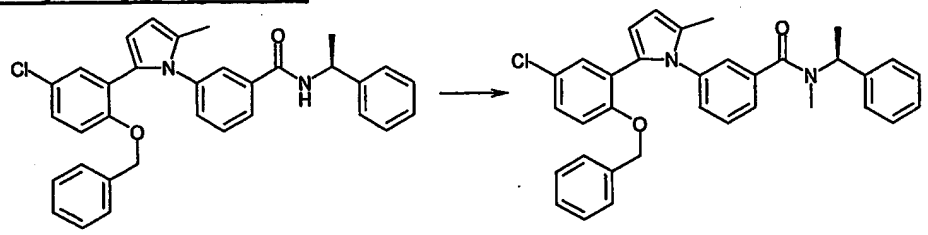
Example 106 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-[(*S*)-1-phenyl-ethyl]-benzamide



Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-[(*R*)-1-phenyl-ethyl]-benzamide using the appropriate benzoic acid.

LC/MS t=4.08 min [MH+] 521/523.

Example 107 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-methyl-*N*-[(*S*)-1-phenyl-ethyl]-benzamide



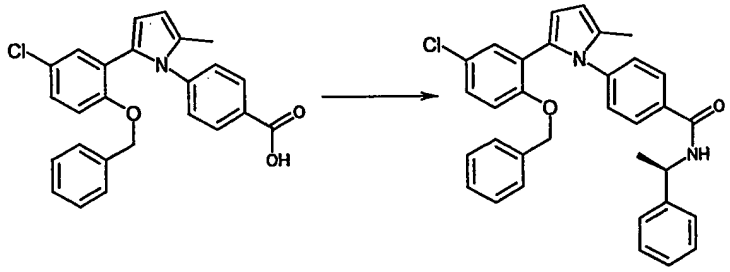
Procedure as for 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-methyl-*N*-[(*R*)-1-phenyl-ethyl]-benzamide using the appropriate benzamide.
LC/MS t=4.13 min [MH+] 535/537.

Example 108 4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-[(*R*)-1-phenyl-ethyl]-benzamide

a) 4-{2-[5-Chloro-2-(benzoxy)-phenyl]-5-methyl-pyrrol-1yl]- benzoic acid ethyl ester
1-[5-Chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione (0.50g, 1.58mmol, 1eq) was heated with ethyl-3-aminobenzoate (0.313g, 1.90mmol, 1.2eq), in a sealed vessel, to 150°C for 24 hours. The reaction mixture was allowed to warm to room temp and diluted with ethylacetate and washed with 2M HCl, the combined organics were washed with brine and dried ($MgSO_4$) and volatiles removed *in-vacuo*. The residue was purified by chromatography on silica gel with 5% EtOAc:*iso*-hexane as the eluant to yield the title compound (0.32g, 0.72mmol, 45%) as a pale yellow solid.
LC/MS t=4.23 min [MH+] 446/448.

b) 4-{2-[5-Chloro-2-(benzoxy)-phenyl]-5-methyl-pyrrol-1yl}- benzoic acid
Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1l^6-isothiazolidin-2-yl)-benzoic acid.
LC/MS t=3.98 min [MH+] 432/434

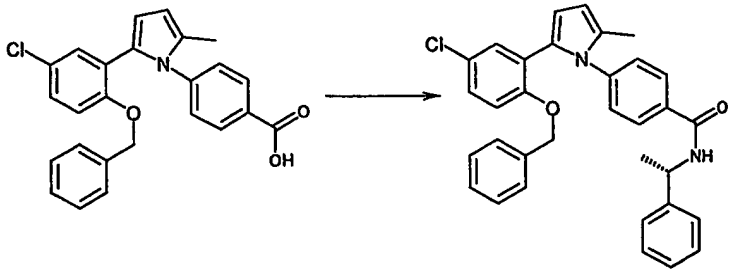
c) 4-[2-(5-Chloro-2-benzyloxy-phenyl)-5-methyl-pyrrol-1yl]-*N*-[(*R*)-1-phenyl-ethyl]-benzamide



Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-[(*R*)-1-phenyl-ethyl]-benzamide using the appropriate benzoic acid.
^{1}H NMR (400MHz, $CDCl_3$) 1.61 (3H, d, J=7Hz), 2.13 (3H, s), 4.71 (2H, s), 5.32 (1H, m), 6.12 (1H, d, J=3Hz), 6.23 (1H, d, J=8Hz), 6.30 (1H, d, J=3Hz), 6.54 (1H, d, J=8H), 6.95-7.07 (5H, m), 7.20-7.41 (9H, m), 7.60 (1H, d, J=8Hz).

LC/MS t=4.09 min [MH+] 521/523.

Example 109 4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-[(*S*)-1-phenyl-ethyl]-benzamide

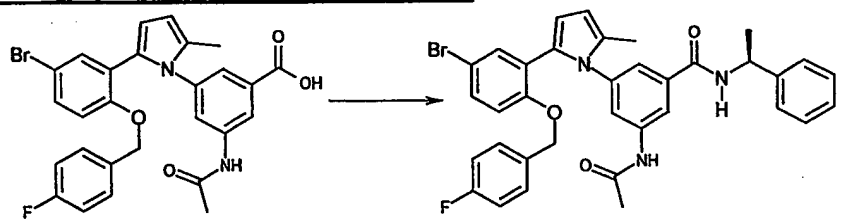


Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-[(*R*)-1-phenyl-ethyl]-benzamide using the appropriate benzoic acid.

^{1}H NMR (400MHz, $CDCl_3$) 1.61 (3H, d, J=7Hz), 2.13 (3H, s), 4.71 (2H, s), 5.23-5.42 (1H, m), 6.12 (1H, d, J=3Hz), 6.23 (1H, d, J=8Hz), 6.30 (1H, d, J=3Hz), 6.54 (1H, d, J=8H), 6.95-7.07 (5H, m), 7.20-7.41 (9H, m), 7.60 (1H, d, J=8Hz).

LC/MS t=4.09 min [MH+] 521/523.

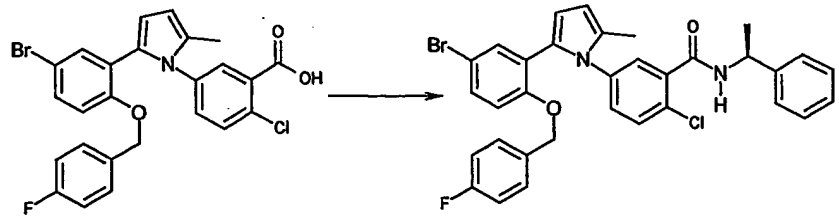
Example 110 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-5-acetylamino-*N*-[(*S*)-1-phenyl-ethyl]-benzamide



Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-[(*R*)-1-phenyl-ethyl]-benzamide using the appropriate benzoic acid.

LC/MS t=3.90 min [MH+] 640/642.

Example 111 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-6-chloro-*N*-[(*S*)-1-phenyl-ethyl]-benzamide

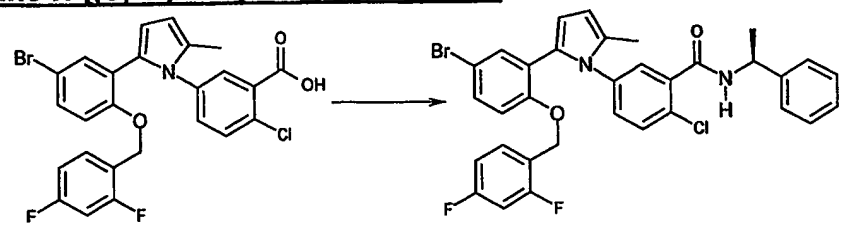


Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-[(*R*)-1-phenyl-ethyl]-benzamide using the appropriate benzoic acid.

^{1}H NMR (400MHz, $CDCl_3$) 1.51 (3H, d, J=7Hz), 2.143 (3H, s), 4.72 (2H, s), 5. 17-5.26 (1H, m), 5.89 (1H, d, J=8Hz), 6.11 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.47 (1H, d, J=8H), 6.88-6.99 (5H, m), 7.16 (1H, dd, J=8Hz, 2Hz), 7.22-7.40 (7H, m).

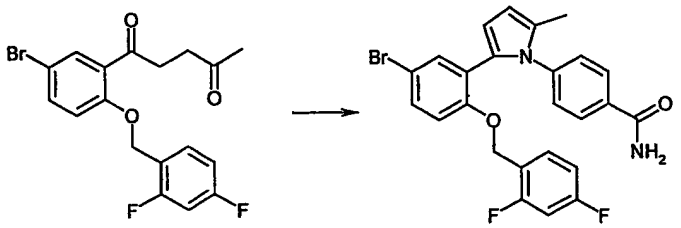
LC/MS t=4.16 min [MH+] 617/619.

Example 112 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-5-acetylamino-*N*-[(*S*)-1-phenyl-ethyl]-benzamide



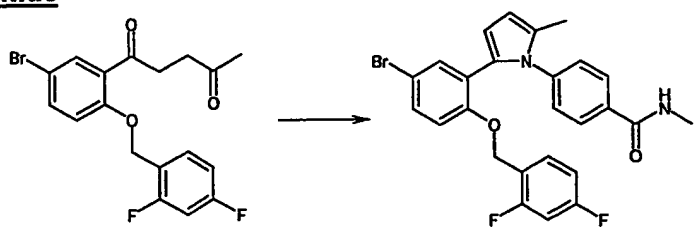
Procedure as for 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-*N*-[(*R*)-1-phenyl-ethyl]-benzamide using the appropriate benzoic acid.
^{1}H NMR (400MHz, $CDCl_3$) 1.53 (3H, d, J=7Hz), 2.15 (3H, s), 4.78 (2H, s), 5. 19-5.27 (1H, m), 6.02 (1H, d, J=8Hz), 6.10 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.52 (1H, d, J=8H), 6.70-6.98 (5H, m), 7.18 (1H, dd, J=8Hz, 2Hz), 7.22-7.40 (6H, m).
LC/MS t=4.18 min [MH+] 635/637.

Example 113 4-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzamide



1-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.10g, 0.25mmol), 4-amino-benzamide (0.041g, 0.3mmol) and *p*-TSA (0.009g, 0.05mmol) were refluxed in toluene (1.5ml) for 18 hours under a nitrogen atmosphere. The solvent was removed *in vacuo* and the resultant residue purified by MDAP. This yielded a white solid (0.013g, 10.4%)
^{1}H-NMR (400MHz, $CDCl_3$,) 2.16 (3H, s), 4.72 (2H, s), 6.13 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.55 (1H, d, J=9Hz), 6.77-6.84 (2H, m), 6.89-6.96 (1H, m), 7.03 (2H, d, J=9Hz), 7.23 (1H, dd, J=3Hz, 9Hz), 7.36 (1H, d, J=3Hz), 7.68 (2H, d, J=9Hz).
LC/MS t=3.75min [MH^+] 497/499.

Example 114 4-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-methyl-benzamide

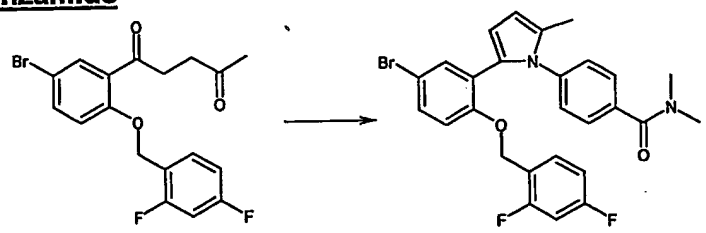


Procedure as for 4-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzamide using the appropriate amine to give title compound.

^{1}H-NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 3.01 (3H, d, J=5Hz), 4.72 (2H, s), 6.03-6.09 (1H, m), 6.12 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.55 (1H, d, J=9Hz), 6.80 (2H, t, J=9Hz), 6.92-6.99 (1H, m), 7.01 (2H, d, J=9Hz), 7.22 (1H, dd, J=3Hz, 9Hz), 7.34 (1H, d, J=3Hz), 7.62 (2H, d, J=9Hz).

LC/MS t=3.86 min [MH^+] 511/513.

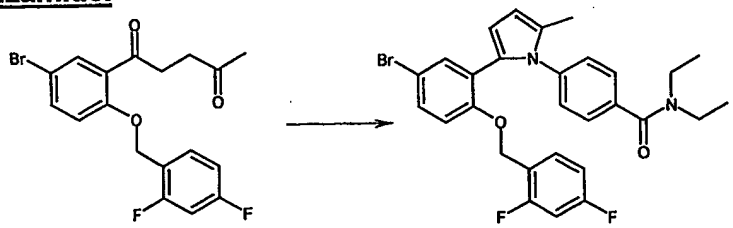
Example115 4-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N,N*-dimethyl-benzamide



Procedure as for 4-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzamide using the appropriate amine to give title compound.

LC/MS t=3.91 min [MH^+] 525/527.

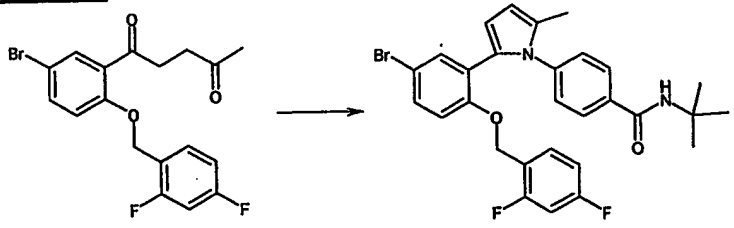
Example 116 4-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N,N*-diethyl-benzamide.



Procedure as for 4-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzamide using the appropriate amine to give title compound.

LC/MS t=4.09 min [MH^+] 553/555.

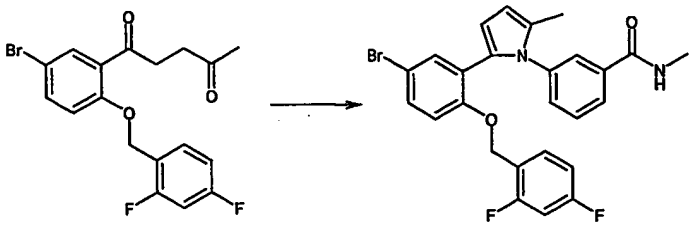
Example 117 4-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N-tert*-butyl-benzamide



Procedure as for 4-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzamide using the appropriate amine to give title compound.

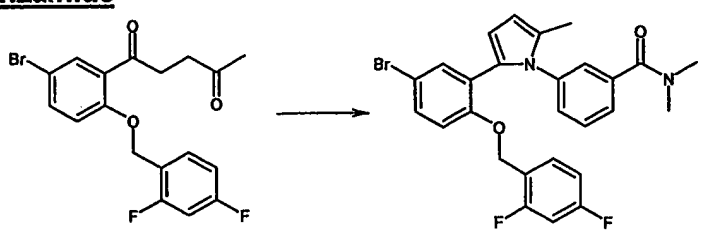
LC/MS t=4.18 min [MH^+] 553/555.

Example 118 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-methyl-benzamide



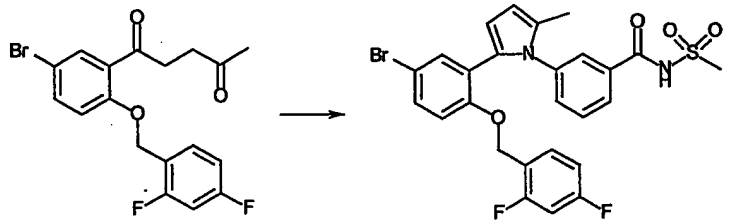
Procedure as for 4-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzamide using the appropriate amine to give title compound.
LC/MS t=3.86 min [MH^+] 511/5136.

Example119 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N,N*-dimethyl-benzamide



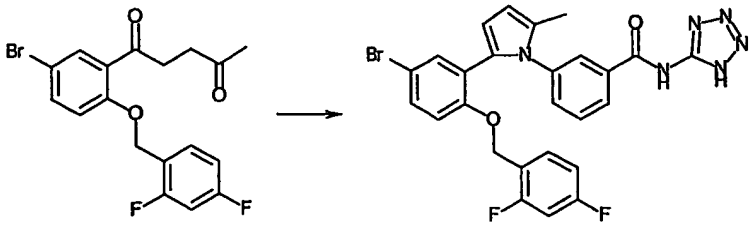
Procedure as for 4-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzamide using the appropriate amine to give title compound.
^{1}H-NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 2.56 (3H, s), 3.02 (3H, s), 4.82 (2H, s), 6.10 (1H, d, J=3Hz), 6.33 (1H, d, J=3Hz), 6.59 (1H, d, J=9Hz), 6.78-6.86 (2H, m), 6.91-6.94 (1H, m), 7.06-7.13 (2H, m), 7.17 (1H, dd, J=3Hz, 9Hz), 7.24 (1H, d, J=3Hz), 7.31-7.38 (2H, m).
LC/MS t=3.90 min [MH^+] 525.

Example 120 3-{-2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(1-methylsulfonyl)-benzamide



Preparation as for 2-(3-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-phenyl)-1*H*-benzoimidazole (81mg, 56%) using the appropriate amine (JP6042371).
^{1}H NMR (400MHz, $CDCl_3$) 2.14 (3H, s), 3.40 (3H, s), 4.76 (2H, s), 6.13 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.62 (1H, d, J=8Hz), 6.82 (2H, m), 7.06 (1H, m), 7.23 (2H, m), 7.31 (1H, d, J=3Hz), 7.38 (1H, t, J=8Hz), 7.49 (1H, bs), 7.67 (1H, bd, J=8Hz), 8.21 (1H, s).
LC/MS t= 4.04 min [MH+] 575/577.

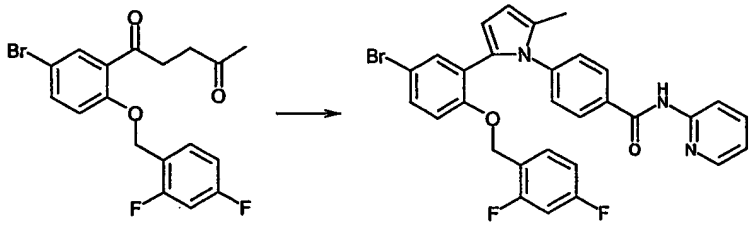
Example 121 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-N-(1H-tetrazol-5-yl)-benzamide



Preparation as for 2-(3-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-phenyl)-1*H*-benzoimidazole using the appropriate amine (Oku *et al*, WO9613485) (17mg, 12%).

^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H,s), 4.75(2H, s), 6.14 (1H,d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.58 (1H, d, J=8Hz), 6.70-6.84(2H, m), 7.01-7.09 (1H, m), 7.20-7.25 (2H, m), 7.30-7.35 (2H, m), 7.43 (1H, t, J=8Hz), 7.75 (1H, s), 8.00 (1H, d, J=8Hz)

Example 122 4-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-*N*-pyridin-2-yl-benzamide



Preparation as for 2-(3-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-phenyl)-1*H*-benzoimidazole using the appropriate amine (23mg, 16%).

^{1}H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.71 (2H, s), 6.13 (1H, m), 6.30 (1H, d, J=4Hz), 6.57 (1H, d, J=10Hz), 6.77-6.85 (2H, m), 6.94-7.02 (1H, m), 7.04-7.10 (2H, m), 7.13-7.18 (1H, m), 7.22-7.28 (1H, m), 7.38 (1H, d, J=2Hz), 7.82-7.90 (3H, m), 8.25-8.30 (1H, m), 8.49 (1H, d, J=8Hz), 9.34 (1H, bs).

LC/MS t= 4.11 min [MH+] 574/576.

Example 123 2-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid

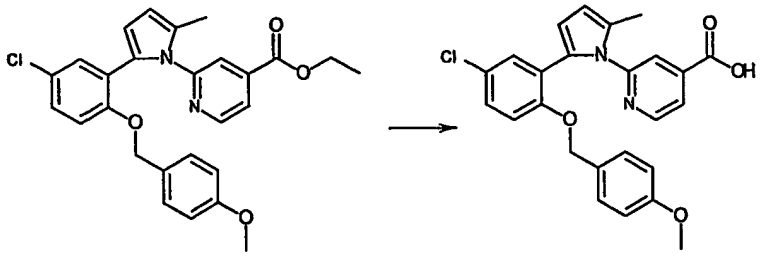
a) 2-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester

1-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-pentane-1,4-dione (1.04g, 2.9mmol) and 2-amino-isonicotinic acid ethyl ester (0.54g, 3.2mmol) (Linschoten *et al*, WO0066557) were heated in toluene (0.5ml) in a sealed vessel at 150°C for 12 hours. Upon cooling, the residue was purified by chromatography on silica gel with isohexane / EtOAc (15%) as eluant, to give the title compound (510mg, 36%).

^{1}H NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7.5Hz), 2.29 (3H, s), 3.79 (3H, s), 4.29 (2H, q, J=7.5Hz), 4.59 (2H, s), 6.12 (1H, d, J=3.5Hz), 6.32 (1H, d, J=3.5Hz), 6.58 (1H, broad d, J=9Hz), 6.79 (2H, d, J=8.5Hz), 6.98 (2H, d, J=8.5Hz), 7.05 (1H, dd, J=3, 9Hz), 7.26 (1H, d, under $CDCl_3$), 7.40 (1H, broad s), 7.66 (1H, dd, J=1.5, 7Hz), 8.52 (1H, d, J=7Hz).

LC/MS t=4.01 min [MH+] 477/479

b) 2-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid



2-{2-[5-Chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester (30mg, 0.06mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (20mg, 71%).

^{1}H NMR (400MHz, d_6-DMSO) 2.19 (3H, s), 3.73 (3H, s), 4.64 (2H, s), 6.07 (1H, broad d, J=3Hz), 6.25 (1H, d, J=3Hz), 6.83-6.88 (3H, m), 7.02 (2H, d, J=9Hz), 7.08 (1H, d, J=3Hz), 7.19 (1H, dd, J=3, 9Hz), 7.32 (1H, s), 7.71 (1H, dd, J=1.5, 5Hz), 8.58 (1H, d, J=5Hz), 13.62 (1H, broad s).

LC/MS t=4.00 min [MH-] 447/449

Example 124 2-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid

a) 2-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester

HCl (4M in dioxane, 2.5ml, 10mmol) was added to 2-{2-[5-chloro-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid (480mg, 1mmol) and stirred at room temperature for 15 minutes. The reaction was concentrated and the residue partitioned between CH_2Cl_2 and $NaHCO_3$. The organics were washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (20-30%) as eluant, to give the title compound (300mg, 84%).

^{1}H NMR (400MHz, $CDCl_3$) 1.37 (3H, t, J=7Hz), 2.24 (3H, s), 4.38 (2H, q, J=7Hz), 6.17 (1H, broad s), 6.27 (1H, d, J=3.5Hz), 6.84 (1H, d, J=9Hz), 6.93 (1H, broad s), 7.09 (1H, broad d, J=9Hz), 7.30 (1H, broad d, J=9Hz), 7.47 (1H, broad s), 7.62 (1H, broad s), 7.82 (1H, broad d, J=5Hz).

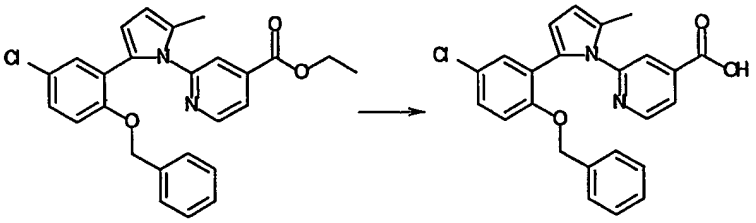
LC/MS t=3.56 min [MH+] 357/359

b) 2-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester

Benzyl bromide (0.013ml, 0.11mmol) was added to 2-{2-[5-chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester (40mg, 0.11mmol) and K_2CO_3 (31mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (10%) as eluant, to give the title compound (35mg, 70%).

^{1}H NMR (400MHz, $CDCl_3$) 1.30 (3H, t, J=7Hz), 2.30 (3H, s), 4.29 (2H, q, J=7Hz), 4.67 (2H, s), 6.13 (1H, d, J=3Hz), 6.33 (1H, d, J=3Hz), 6.56 (1H, d, J=9Hz), 7.02-7.07 (3H, m), 7.22-7.29 (4H, m), 7.40 (1H, s), 7.66 (1H, dd, J=1.5, 5Hz), 8.52 (1H, d, J=5Hz).
LC/MS t=4.03 min [MH+] 447/449

c) 2-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid



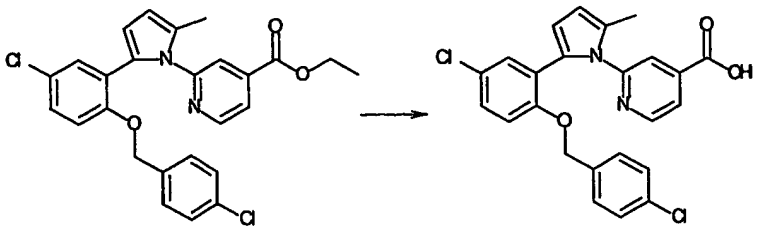
2-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester (35mg, 0.08mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (28mg, 85%).
^{1}H NMR (400MHz, *d*6-DMSO) 2.20 (3H, s), 4.73 (2H, s), 6.09 (1H, broad d, J=3.5Hz), 6.28 (1H, d, J=3.5Hz), 6.85 (1H, d, J=9Hz), 7.06 (2H, dd, J=1.5, 8Hz), 7.10 (1H, d, J=3Hz), 7.19 (1H, dd, J=3, 9Hz), 7.25-7.32 (3H, m), 7.33 (1H, s), 7.72 (1H, dd, J=1.5, 5Hz), 8.58 (1H, d, J=5Hz), 13.58 (1H, broad s).
LC/MS t=4.02 min [MH+] 419/421

<u>Example 125 2-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid</u>

a) 2-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester

4-Chloro-benzyl bromide (23mg, 0.11mmol) was added to 2-{2-[5-chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester (40mg, 0.11mmol) and K_2CO_3 (31mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (10%) as eluant, to give the title compound (47mg, 87%).
^{1}H NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7Hz), 2.30 (3H, s), 4.30 (2H, q, J=7Hz), 4.61 (2H, s), 6.13 (1H, d, J=3.5Hz), 6.31 (1H, d, J=3.5Hz), 6.54 (1H, d, J=9Hz), 6.99 (2H, d, J=8.5Hz), 7.06 (1H, dd, J=2.5, 9Hz), 7.24 (2H, d, J=8.5Hz), 7.29 (1H, d, J=2.5Hz), 7.38 (1H, s), 7.66 (1H, dd, J=1.5, 5Hz), 8.50 (1H, d, J=5Hz).
LC/MS t=4.16 min [MH+] 481/483/485.

b) 2-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid



2-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester (47mg, 0.10mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (35mg, 79%).

^{1}H NMR (400MHz, *d*6-DMSO) 2.20 (3H, s), 4.72 (2H, s), 6.09 (1H, dd, J=3.5Hz), 6.28 (1H, d, J=3.5Hz), 6.84 (1H, d, J=9Hz), 7.09 (2H, d, J=8.5Hz), 7.12 (1H, d, J=3Hz), 7.20 (1H, dd, J=3, 9Hz), 7.32 (1H, s), 7.35 (2H, d, J=8.5Hz), 7.70 (1H, dd, J=1.5, 5Hz), 8.57 (1H, d, J=5Hz), 13.50 (1H, broad s).

LC/MS t=4.24 min [MH+] 453/455/457.

Example 126 2-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid

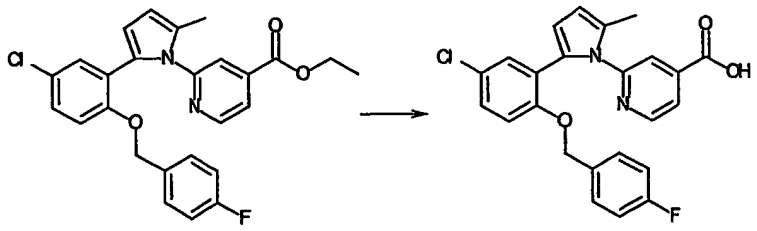
a) 2-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester

4-Fluoro-benzyl bromide (0.014ml, 0.11mmol) was added to 2-{2-[5-chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester (40mg, 0.11mmol) and K_2CO_3 (31mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (10%) as eluant, to give the title compound (40mg, 77%).

^{1}H NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7Hz), 2.30 (3H, s), 4.30 (2H, q, J=7Hz), 4.61 (2H, s), 6.13 (1H, d, J=3.5Hz), 6.31 (1H, d, J=3.5Hz), 6.57 (1H, d, J=9Hz), 6.92-7.09 (5H, m), 7.29 (1H, d, J=2.5Hz), 7.37 (1H, broad s), 7.65 (1H, dd, J=1.5, 5Hz), 8.50 (1H, d, J=5Hz).

LC/MS t=4.03 min [MH+] 465/467.

b) 2-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid



2-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester (40mg, 0.09mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (33mg, 88%).

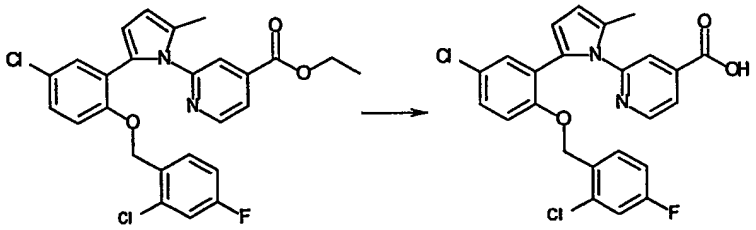
^{1}H NMR (400MHz, *d*6-DMSO) 2.20 (3H, s), 4.70 (2H, s), 6.09 (1H, broad d, J=3.5Hz), 6.27 (1H, d, J=3.5Hz), 6.87 (1H, d, J=9Hz), 7.10-7.14 (5H, m), 7.21 (1H, dd, J=3, 9Hz), 7.30 (1H, broad s), 7.70 (1H, dd, J=3.5, 5Hz), 8.56 (1H, d, J=5Hz), 13.70 (1H, broad s).
LC/MS t=4.03 min [MH+] 437/439.

Example 127 2-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid

a) 2-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester

2-Chloro-4-fluoro-benzyl bromide (25mg, 0.11mmol) was added to 2-{2-[5-chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester (40mg, 0.11mmol) and K_2CO_3 (31mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (10%) as eluant, to give the title compound (46mg, 82%).
^{1}H NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7Hz), 2.31 (3H, s), 4.30 (2H, q, J=7Hz), 4.68 (2H, s), 6.14 (1H, dd, J=1, 3.5Hz), 6.33 (1H, d, J=3.5Hz), 6.57 (1H, d, J=9Hz), 6.90 (1H, ddd, J=2.5, 9Hz), 7.03-7.11 (3H, m), 7.30 (1H, d, J=2.5Hz), 7.40 (1H, broad s), 7.67 (1H, dd, J=1.5, 5Hz), 8.50 (1H, d, J=5Hz).
LC/MS t=4.20 min [MH+] 499/501/503

b) 2-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid



2-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester (46mg, 0.09mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (40mg, 92%).
^{1}H NMR (400MHz, *d*6-DMSO) 2.19 (3H, s), 4.73 (2H, s), 6.09 (1H, d, J= 3.5Hz), 6.29 (1H, d, J=3.5Hz), 6.92 (1H, d, J=9Hz), 7.11 (1H, d, J=2.5Hz), 7.11-7.25 (3H, m), 7.29 (1H, s), 7.44 (1H, dd, J=2.5, 9Hz), 7.70 (1H, dd, J=1.5, 5Hz), 8.53 (1H, d, J=5Hz), 13.60 (1H, broad s).
LC/MS t=4.28 min [MH-] 469/471/473.

Example 128 2-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid

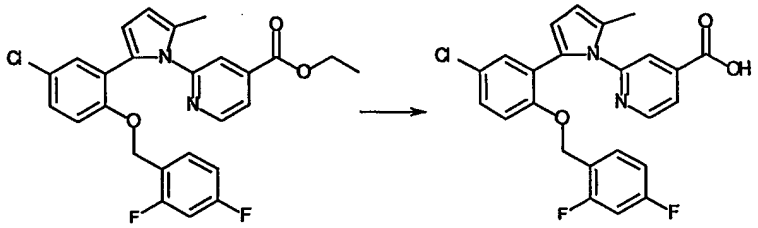
a) 2-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester

2,4-Difluoro-benzyl bromide (0.015ml, 0.11mmol) was added to 2-{2-[5-chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester (40mg, 0.11mmol) and K_2CO_3 (31mg, 0.31mmol) in DMF (1ml) and the reaction mixture was heated at 60°C for 16 hours. Upon cooling the reaction mixture was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel with isohexane / EtOAc (10%) as eluant, to give the title compound (44mg, 81%).

^{1}H NMR (400MHz, $CDCl_3$) 1.32 (3H, t, J=7Hz), 2.30 (3H, s), 4.30 (2H, q, J=7Hz), 4.67 (2H, s), 6.12 (1H, dd, J=1, 3.5Hz), 6.31 (1H, d, J=3.5Hz), 6.61 (1H, d, J=9Hz), 6.71-6.83 (2H, m), 7.02-7.11 (2H, m), 7.27 (1H, d, J=2.5Hz), 7.39 (1H, s), 7.66 (1H, dd, J=1.5, 5Hz), 8.50 (1H, d, J=5Hz).

LC/MS t=4.08 min [MH+] 483/485

b) 2-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid



2-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester (44mg, 0.09mmol) was heated at reflux in a 1:1 mixture of ethanol/2M NaOH (2ml) in a sealed vessel for 1.5 hours. Upon cooling, the reaction was diluted with ethyl acetate, washed with 2M HCl and brine, dried ($MgSO_4$) and concentrated to give the title compound (38mg, 92%).

^{1}H NMR (400MHz, *d*6-DMSO) 2.17 (3H, s), 4.72 (2H, s), 6.07 (1H, broad d, J=3.5Hz), 6.26 (1H, d, J=3.5Hz), 6.96 (1H, d, J=9Hz), 7.03 (1H, ddd, J=2.5, 9Hz), 7.10 (1H, d, J=2.5Hz), 7.12-7.26 (3H, m), 7.27 (1H, s), 7.69 (1H, dd, J=1.5, 5Hz), 8.53 (1H, d, J=5Hz), 13.60 (1H, broad s).

LC/MS t=4.06 min [MH+] 455/457

<u>Example 129 5-{2-[2-(Benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid</u>

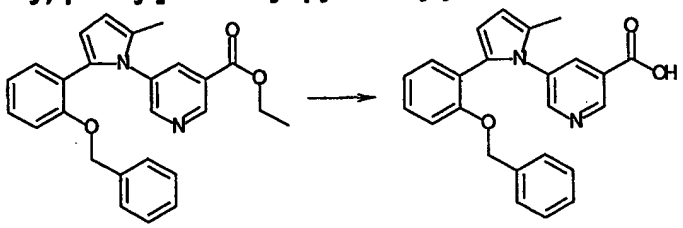
a) 5-{2-[2-(Benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

5-{2-[2-(Hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.116g, 0.358mmol), benzyl bromide (0.064ml, 0.537mmol) and potassium carbonate (0.099g, 0.716mmol) were heated in DMF (1ml) at 65°C in a nitrogen atmosphere for 3 hours. Upon cooling the mixture was diluted with EtOAc and water. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organics were then washed with brine and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 15% EtOAc/iso-hexane. This yielded the title compound as a yellow oil (0.041g, 28%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.32 (3H, t, J=7Hz), 2.17 (3H, s), 4.31 (2H, q, J=7Hz), 4.75 (2H, s), 6.17 (1H, dd, J=1Hz, 3Hz), 6.32 (1H, d, J=3Hz), 6.67 (1H, d, 9Hz), 6.91 (1H, ddd, J=1Hz, 7Hz), 7.07 (2H, dd, J=2Hz, 9Hz), 7.14 (1H, ddd, J=2Hz, 7Hz), 7.28-7.32 (4H, m), 7.90 (1H, t, J=2Hz), 8.37 (1H, d, J=2Hz), 9.02 (1H, d, J=2Hz).

LC/MS t = 3.78 min [MH^+] 413

b) 5-{2-[2-(Benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[2-(Benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.041g), 2M NaOH (1ml) and EtOH (2ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated by nitrogen blowdown, to yield the title compound as an orange solid (0.038g, 99%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.74 (2H, s), 6.18 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.68 (1H, d, J=9Hz), 6.91 (1H, t, J=8Hz), 7.08 (2H, broad d, J=8Hz), 7.13 (1H, ddd, J=2Hz, 8Hz), 7.21-7.30 (4H, m), 7.98 (1H, t, J=2Hz), 8.37 (1H, d, J=2Hz), 9.07 (1H, d, J=2Hz).

LC/MS t = 3.70 min [MH^+] 385

<u>Example 130 5-{2-[2-(2-Chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid</u>

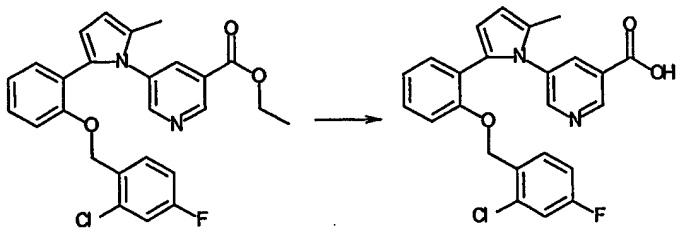
a) 5-{2-[2-(2-Chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

5-{2-[2-(Hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.116g, 0.358mmol), 2-chloro-4-fluorobenzyl bromide (0.120g, 0.537mmol) and potassium carbonate (0.099g, 0.716mmol) were heated in DMF (1ml) at 65°C in a nitrogen atmosphere for 3 hours. Upon cooling the mixture was diluted with EtOAc and water. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organics were then washed with brine and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 15% EtOAc/iso-hexane. This yielded the title compound as a yellow oil (0.035g, 30%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.33 (3H, t, J=7Hz), 2.18 (3H, s), 4.32 (2H, q, J=7Hz), 4.78 (2H, s), 6.18 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.65 (1H, d, 9Hz), 6.89-7.01 (3H, m), 7.07-7.18 (2H, m), 7.29 (1H, d, J=2Hz), 7.93 (1H, t, J=2Hz), 8.40 (1H, d, J=2Hz), 9.03 (1H, d, J=2Hz).

LC/MS t = 3.96 min [MH^+] 465

b) 5-{2-[2-(2-Chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[2-(2-Chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.035g), 2M NaOH (1ml) and EtOH (2ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated by nitrogen blowdown, to yield the title compound as a yellow solid (0.029g, 89%).

^{1}H-NMR (400MHz, MeOD) 2.15 (3H, s), 4.75 (2H, s), 6.13 (1H, d, J=3Hz), 6.21 (1H, d, J=3Hz), 6.80 (1H, d, J=9Hz),6.98 (1H, t, J=8Hz), 7.03 (1H, ddd, J=2Hz, 8Hz), 7.08-7.13 (1H, m), 7.17-7.24 (2H, m), 7.32 (1H, dd, J=1Hz, 7Hz), 7.91 (1H, t, J=1Hz), 8.22 (1H, d, J=1Hz), 8.91 (1H, broad s).

LC/MS t = 3.96 min [MH^+] 437.

Example 131 5-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

a) 5-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

5-{2-[5-Bromo-2-(4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (1.7g, 3.26mmol) was stirred at room temperature and under nitrogen in 4.0M hydrogen chloride in dioxane (15ml) for 20 minutes. The solvent was then removed in vacuo and the residue diluted with EtOAc. The solution was then washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant oil was purified by chromatography on silica gel eluting with 30% EtOAc/iso-hexane. This yielded the title compound as a yellow oil (0.361g, 27%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.40 (3H, t, J=7Hz), 2.18 (3H, s), 4.41 (2H, q, J=7Hz), 5.83 (1H, s), 6.20 (1H, d, J=3Hz), 6.38 (1H, d, J=3Hz), 6.72 (1H, d, J=9Hz), 6.95 (1H, d, 3Hz), 7.19 (1H, dd, J=3Hz, 9Hz), 8.05 (1H, t, J=2Hz), 8.49 (1H, d, J=3Hz), 9.13 (1H, d, J=2Hz).

LC/MS t = 3.51 min [MH^+] 401/403.

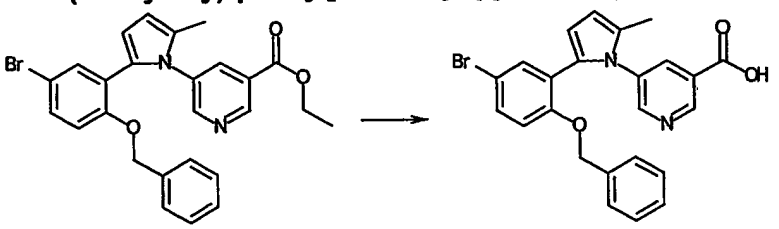
b) 5-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

5-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.06g, 0.125mmol), benzyl bromide (0.022ml, 0.187mmol) and potassium carbonate (0.034g, 0.249mmol) were heated in DMF (1ml) at 65°C in a nitrogen atmosphere for 2.5 hours. Upon cooling the mixture was diluted with EtOAc and water. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organics were then washed with brine and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 15% EtOAc/iso-hexane. This yielded the title compound as a yellow oil (0.057g, 77%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.34 (3H, t, J=7Hz), 2.15 (3H, s), 4.32 (2H, q, J=7Hz), 4.69 (2H, s), 6.17 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.53 (1H, d, 9Hz), 7.02 (2H, m), 7.22 (1H, dd, J=3Hz, 9Hz), 7.29 (3H, m), 7.45 (1H, d, J=3Hz), 7.89 (1H, t, J=2Hz), 8.36 (1H, d, J=2Hz), 9.05 (1H, d, J=2Hz).

LC/MS t = 3.99 min [MH^+] 491/493.

c) 5-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



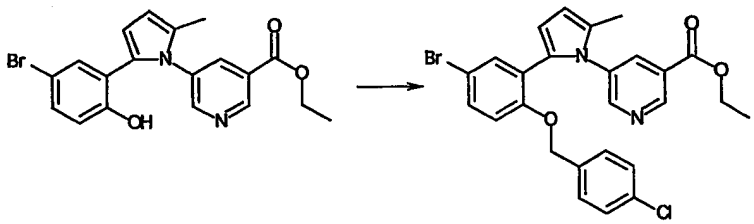
5-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.057g), 2M NaOH (1.5ml) and EtOH (2.5ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated by nitrogen blowdown, to yield the title compound as an off white solid (0.053g, 99%).

^{1}H-NMR (400MHz, MeOD) 2.13 (3H, s), 4.70 (2H, s), 6.14 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.73 (1H, d, 9Hz), 7.08 (2H, dd, J=1Hz, 8Hz), 7.25-7.32 (4H, m), 7.44 (1H, d, J=2Hz), 7.91 (1H, t, J=2Hz), 8.23 (1H, d, J=2Hz), 8.93 (1H, d, J=1Hz).

LC/MS t = 4.00 min [MH^+] 463/465.

<u>Example 132 5-{2-[5-Bromo-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid</u>

a) 5-{2-[5-Bromo-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester



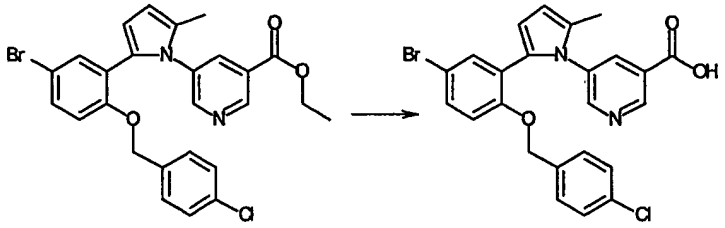
5-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.06g, 0.125mmol), 4-chlorobenzyl bromide (0.038g, 0.187mmol) and potassium carbonate (0.034g, 0.249mmol) were heated in DMF (1ml) at 65°C in a nitrogen atmosphere for 2.5 hours. Upon cooling the mixture was diluted with EtOAc and water. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organics were then washed with brine and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 15% EtOAc/iso-hexane. This yielded the title compound as a yellow oil (0.080g, 100%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.35 (3H, t, J=7Hz), 2.16 (3H, s), 4.34 (2H, q, J=7Hz), 4.65 (2H, s), 6.17 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.50 (1H, d, 9Hz), 6.98 (2H, d, J=9Hz), 7.23

(1H, d, J=3Hz), 7.25-7.29 (2H, m), 7.46 (1H, d, J=3Hz), 7.87 (1H, t, J=2Hz), 8.36 (1H, d, J=2Hz), 9.04 (1H, d, J=2Hz).

LC/MS t = 4.13 min [MH^+] 527.

b) 5-{2-[5-Bromo-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[5-Bromo-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.080g), 2M NaOH (1.5ml) and EtOH (2.5ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated by nitrogen blowdown, to yield the title compound as an off white solid (0.056g, 73%).

^{1}H-NMR (400MHz, MeOD) 2.13 (3H, s) 4.71 (2H, s), 6.12 (1H, d, J=3Hz), 6.25 (1H, d, J=3Hz), 6.67 (1H, d, J=9Hz), 7.07 (2H, d, J=8Hz), 7.25 (1H, dd, J=3Hz, 9Hz), 7.30 (2H, d, J=8Hz), 7.38 (1H, d, J=3Hz), 7.97 (1H, t, J=2Hz), 8.17 (1H, d, J=2Hz), 8.97 (1H, d, J=2Hz).

LC/MS t = 4.22 min [MH^+] 497/499.

Example 133 5-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

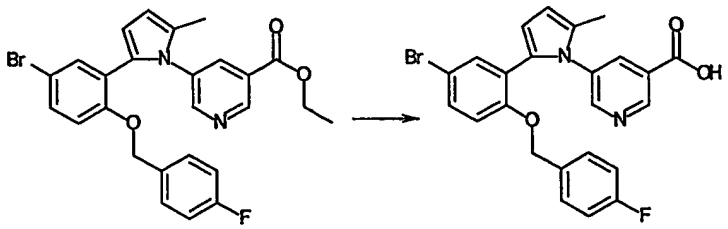
a) 5-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

5-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.06g, 0.125mmol), 4-fluoro-benzyl bromide (0.024ml, 0.187mmol) and potassium carbonate (0.034g, 0.249mmol) were heated in DMF (1ml) at 65°C in a nitrogen atmosphere for 2.5 hours. Upon cooling the mixture was diluted with EtOAc and water. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organics were then washed with brine and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 15% EtOAc/iso-hexane. This yielded the title compound as a yellow oil (0.051g, 67%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.35 (3H, t, J=7Hz), 2.15 (3H, s), 4.33 (2H, q, J=7Hz), 4.63 (2H, s), 6.17 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.52 (1H, d, 9Hz), 6.95-7.04 (4H, m), 7.23 (1H, d, J=2Hz), 7.46 (1H, d, J=2Hz), 7.86 (1H, t, J=2Hz), 8.34 (1H, d, J=2Hz), 9.04 (1H, d, J=2Hz).

LC/MS t = 4.00 min [MH^+] 509/511

b) 5-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.051g), 2M NaOH (1.5ml) and EtOH (2.5ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated by nitrogen blowdown, to yield the title compound as an off white solid (0.043g, 89%).

^{1}H-NMR (400MHz, MeOD) 2.12 (3H, s), 4.69 (2H, s), 6.11 (1H, d, J=3Hz), 6.23 (1H, d, J=3Hz), 6.68 (1H, d, J=9Hz), 7.00-7.07 (2H, m), 7.09-7.15 (2H, m), 7.24 (1H, dd, J=3Hz, 9Hz), 7.38 (1H, d, J=2Hz), 7.97 (1H, t, J=1Hz), 8.14 (1H, d, J=2Hz), 8.95 (1H, broad s).

LC/MS t = 4.00 min [MH^+] 481/483

Example 134 5-{2-[5-Bromo-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

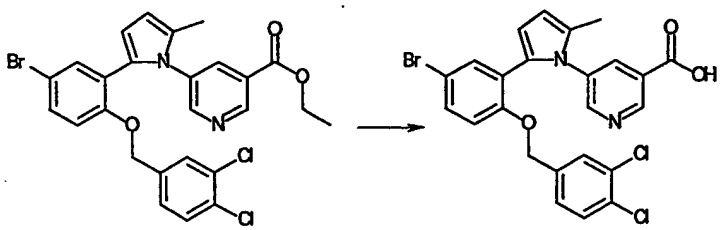
a) 5-{2-[5-Bromo-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

5-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.06g, 0.125mmol), 3,4-dichlorobenzyl bromide (0.032ml, 0.187mmol) and potassium carbonate (0.034g, 0.249mmol) were heated in DMF (1ml) at 65°C in a nitrogen atmosphere for 2.5 hours. Upon cooling the mixture was diluted with EtOAc and water. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organics were then washed with brine and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 15% EtOAc/iso-hexane. This yielded the title compound as a clear oil (0.094g, 100%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.35 (3H, t, J=7Hz), 2.18 (3H, s), 4.33 (2H, q, J=7Hz), 4.64 (2H, s), 6.19 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.49 (1H, d, 9Hz), 6.88 (1H, dd, J=1Hz, 9Hz), 7.10 (1H, d, J=1Hz), 7.24 (1H, d, J=3Hz), 7.38 (1H, d, J=9Hz), 7.48 (1H, d, J=3Hz), 7.90 (1H, t, J=2Hz), 8.39 (1H, d, J=2Hz) 9.0 (1H, d, J=2Hz).

LC/MS t = 4.25 min [MH^+] 561

b) 5-{2-[5-Bromo-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[5-Bromo-2-(3,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.094g), 2M NaOH (1.5ml) and EtOH (2.5ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated by nitrogen blowdown, to yield the title compound as an off white solid (0.091g, 100%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 4.66 (2H, s), 6.16 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.43 (1H, d, 9Hz), 6.88 (1H, dd, J=2Hz, 9Hz), 7.13-7.18 (2H, m), 7.35-7.39 (2H, m), 7.90 (1H, t, J=2Hz), 8.28 (1H, d, J=2Hz) 9.04 (1H, broad s).

LC/MS t = 4.41 min [MH^+] 533.

Example 135 5-{2-[5-Bromo-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

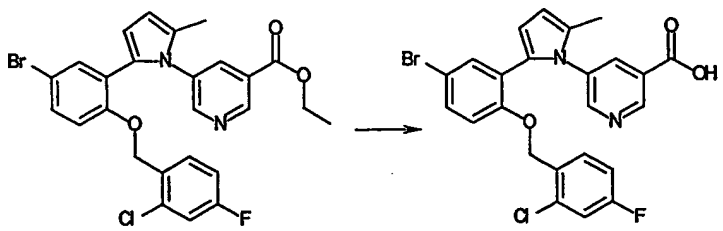
a) 5-{2-[5-Bromo-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

5-[2-(5-Bromo-2-hydroxy-phenyl)-5-methyl-pyrrol-1-yl]-nicotinic acid ethyl ester (0.06g, 0.125mmol), 2-chloro-4-fluoro-benzyl bromide (0.042g, 0.187mmol) and potassium carbonate (0.034g, 0.249mmol) were heated in DMF (1ml) at 65°C in a nitrogen atmosphere for 2.5 hours. Upon cooling the mixture was diluted with EtOAc and water. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organics were then washed with brine and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 15% EtOAc/iso-hexane. This yielded the title compound as a clear oil (0.079g, 98%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.35 (3H, t, J=7Hz), 2.17 (3H, s), 4.34 (2H, q, J=7Hz), 4.72 (2H, s), 6.18 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.51 (1H, d, 9Hz), 6.91 (2H, dd, J=1Hz, 7Hz), 7.09 (1H, dt, J=1Hz, 9Hz), 7.25 (1H, d, J=3Hz), 7.45 (1H, d, J=3Hz), 7.91 (1H, t, J=2Hz), 8.40 (1H, d, J=3Hz), 9.06 (1H, d, J=2Hz).

LC/MS t = 4.14 min [MH^+] 545

b) 5-{2-[5-Bromo-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[5-Bromo-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.079g), 2M NaOH (1.5ml) and EtOH (2.5ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with

3xEtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated by nitrogen blowdown, to yield the title compound as an off white solid (0.057g, 76%).

^{1}H-NMR (400MHz, MeOD) 2.15 (3H, s), 4.78 (2H, s), 6.12 (1H, d, J=3Hz), 6.24 (1H, d, J=3Hz), 6.69 (1H, d, J=9Hz), 7.00-7.06 (2H, m), 7.20 (1H, broad d, J= 9Hz), 7.27 (1H, dd, J=3Hz, 9Hz), 7.39 (1H, d, J=3Hz), 7.99 (1H, t, J=2Hz), 8.20 (1H, d, J=2Hz), 8.98 (1H, broad s).

LC/MS t = 4.22 min [MH^+] 517.

Example 136 5-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid

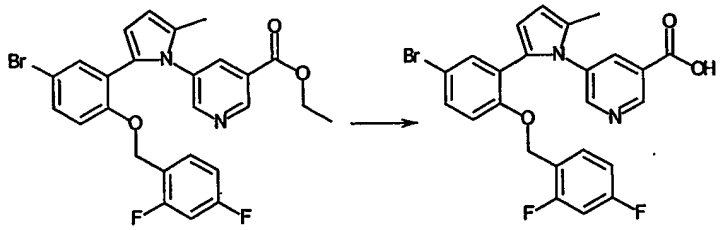
a) 5-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester

5-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.06g, 0.125mmol), 2,4-difluorobenzyl bromide (0.024ml, 0.187mmol) and potassium carbonate (0.034g, 0.249mmol) were heated in DMF (1ml) at 65°C in a nitrogen atmosphere for 2.5 hours. Upon cooling the mixture was diluted with EtOAc and water. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organics were then washed with brine and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 15% EtOAc/iso-hexane. This yielded the title compound as a yellow oil (0.073g, 92%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.37 (3H, t, J=7Hz), 2.16 (3H, s), 4.36 (2H, q, J=7Hz), 4.70 (2H, s), 6.16 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.57 (1H, d, 9Hz), 6.76-6.83 (2H, m), 6.93-7.00 (1H, m), 7.26-7.28 (1H, m), 7.43 (1H, d, J=2Hz), 7.90 (1H, d, J=2Hz), 8.37 (1H, d, J=2Hz), 9.06 (1H, d, J=2Hz).

LC/MS t = 4.01 min [MH^+] 527/529.

b) 5-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid



5-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-nicotinic acid ethyl ester (0.073g), 2M NaOH (1.5ml) and EtOH (2.5ml) were heated at 100°C in a sealed vessel for 1 hour. Upon cooling the mixture was diluted in EtOAc and washed with 0.5M citric acid. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated by nitrogen blowdown, to yield the title compound as an off white solid (0.063g, 92%).

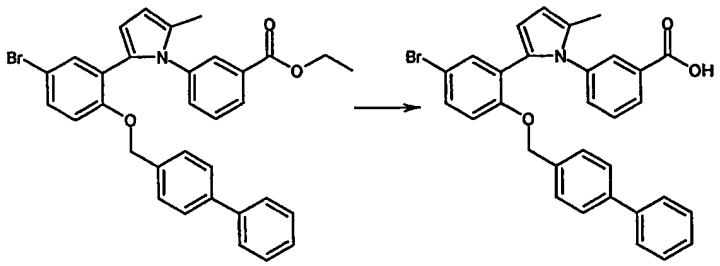
^{1}H-NMR (400MHz, MeOD) 2.12 (3H, s), 4.75 (2H, s), 6.10 (1H, broad s), 6.21 (1H, d, J=3Hz), 6.73 (1H, d, J=9Hz), 6.88-6.97 (2H, m), 7.10 (1H, q, J=7Hz), 7.28 (1H, dd, J=2Hz, 9Hz), 7.35 (1H, broad s), 7.98 (1H, broad s), 8.15 (1H, broad s), 8.96 (1H, broad s).
LC/MS t = 4.00 min [MH$^+$] 499/501.

Example 137 3-{2-[5-Bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.07g, 0.25mmol), 4-bromomethyl-biphenyl (0.074g, 0.3mmol), potassium carbonate (0.069g, 0.5mmol) and DMF (1ml) were stirred under nitrogen at 50°C for 4h. The solvent was then removed by heating under high vacuum. The residue was taken up in DCM, washed with H_2O and the organics separated using a phase separator column, and the solvent removed in vacuo. The residue was then purified by column chromatography on a SPE column (5g) eluting in 10% EtOAc/i-hexane. This yielded the title compound as a clear oil (0.074g, 74%).
LC/MS t=4.45 min [MH$^+$] 566/568.

b) 3-{2-[5-Bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



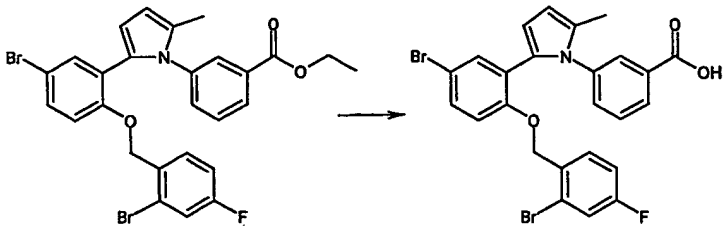
Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.
LC/MS t=4.32 min [MH$^+$] 538/540.

Example 138 3-{2-[5-Bromo-2-(2-bromo-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2-bromo-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.
LC/MS t=4.39 min [MH$^+$] 586/588.

b) 3-{2-[5-Bromo-2-(2-bromo-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.

^{1}H-NMR (400MHz, $CDCl_3$) 2.04 (3H, s), 4.69 (2H, s), 6.07 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.42 (1H, d, J=9Hz), 6.85-6.95 (2H, m), 7.02-7.10 (3H, m), 7.18 (1H, dd, J=2Hz, 8Hz), 7.25-7.28 (1H, m excess), 7.72 (1H, s), 7.81 (1H, d, J=8Hz).

LC/MS t=4.26 min [MH^+] 558/560.

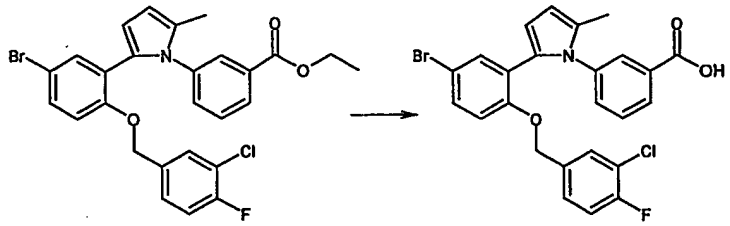
Example 139 3-{2-[5-Bromo-2-(3-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(3-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.

LC/MS t=4.34 min [MH^+] 542/544.

b) 3-{2-[5-Bromo-2-(3-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.

LC/MS t=4.19 min [MH^+] 514/516.

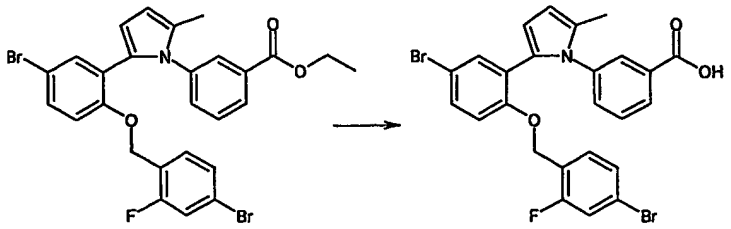
Example 140 3-{2-[5-Bromo-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.

LC/MS t=4.39 min [MH^+] 586/588.

b) 3-{2-[5-Bromo-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.

^{1}H-NMR (400MHz, $CDCl_3$) 2.10 (3H, s), 4.70 (2H, s), 6.10 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.47 (1H, d, J=9Hz), 6.87 (1H, t, J=8Hz), 7.07-7.20 (4H, m), 7.25-7.28 (1H, m excess), 7.31 (1H, d, J=2Hz), 7.73 (1H, t, J=1Hz), 7.87 (1H, dt, J=1Hz, 8Hz).

LC/MS - t=4.25 min [MH^+] 558/560.

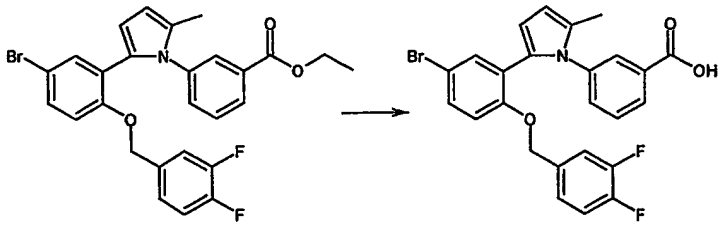
Example 141 3-{2-[5-Bromo-2-(3,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(3,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.

LC/MS t=4.25 min [MH^+] 526/528.

b) 3-{2-[5-Bromo-2-(3,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.

^{1}H-NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.64 (2H, s), 6.14 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.48 (1H, d, J=9Hz), 6.74-6.80 (1H, m), 6.81-6.87 (1H, m), 7.02-7.10 (1H, m), 7.13-7.17 (1H, m), 7.19 (1H, dd, J=3Hz, 9Hz), 7.31 (1H, t, J=8Hz), 7.40 (1H, d, J=2Hz), 7.76 (1H, t, J=1Hz), 7.95 (1H, dt, J=1Hz, 8Hz).

LC/MS t=4.08 min [MH^+] 498/500.

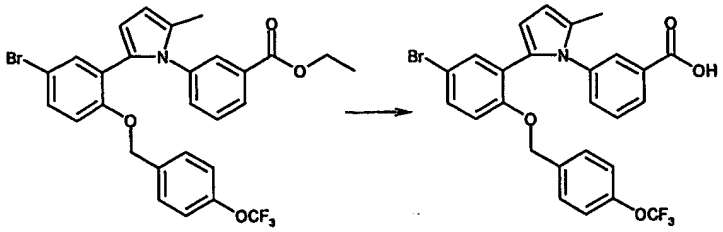
Example 142 3-{2-[5-Bromo-2-(4-trifluoromethoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(4-trifluoromethoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.

LC/MS t=4.36 min [MH^+] 574/576.

b) 3-{2-[5-Bromo-2-(4-trifluoromethoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.

LC/MS t=4.20 min [MH^+] 546/548.

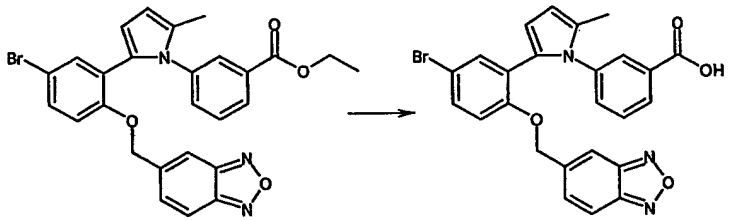
Example 143 3-{2-[5-Bromo-2-(benzo[1,2,5]oxadiazol-5-ylmethoxy)-phenyl]-5-methyl-pyrrol-1- yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(benzo[1,2,5]oxadiazol-5-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.

LC/MS t=4.17 min [MH^+] 532/534.

b) 3-{2-[5-Bromo-2-(benzo[1,2,5]oxadiazol-5-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.

LC/MS t=4.01 min [MH^+] 504/506.

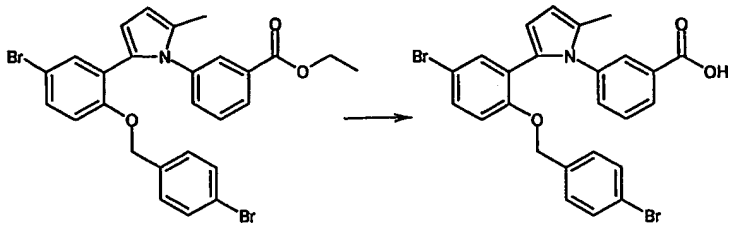
Example 144 3-{2-[5-Bromo-2-(4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.

LC/MS t=4.37 min [MH^+] 568/570

b) 3-{2-[5-Bromo-2-(4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.

^{1}H-NMR (400MHz, $CDCl_3$) 2.09 (3H, s), 4.62 (2H, s), 6.09 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.43 (1H, d, J=9Hz), 6.90 (2H, d, J=8Hz), 7.04-7.12 (2H, m), 7.14-7.21 (1H, m), 7.32 (1H, s), 7.36 (2H, d, J=8Hz), 7.73 (1H, s), 7.87 (1H, d, J=8Hz).

LC/MS t=4.23 min [MH^+] 540/542.

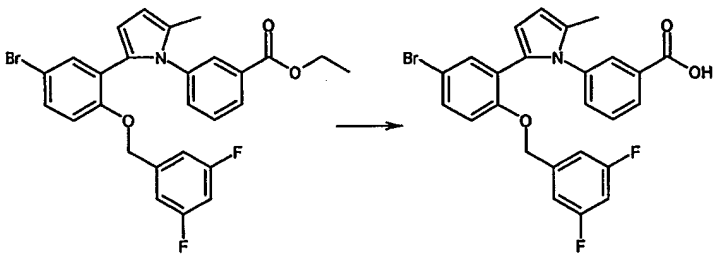
Example 145 3-{2-[5-Bromo-2-(3,5-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(3,5-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.

LC/MS t=4.27 min [MH^+] 526/528.

b) 3-{2-[5-Bromo-2-(3,5-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.

LC/MS t=4.09 min [MH^+] 498/500.

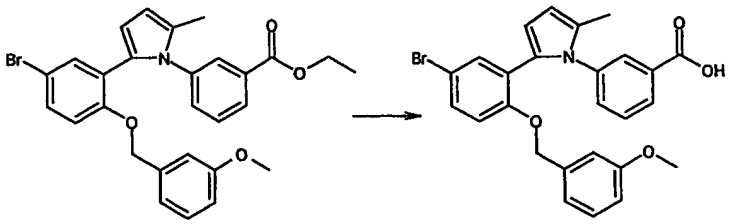
Example 146 3-{2-[5-Bromo-2-(3-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(3-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.

LC/MS t=4.20 min [MH^+] 520/522.

b) 3-{2-[5-Bromo-2-(3-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



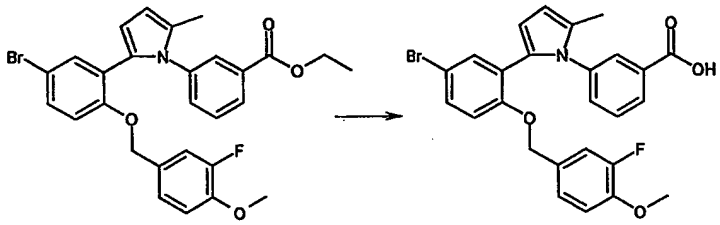
Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.
LC/MS t=4.02 min [MH^+] 492/494.

Example 147 3-{2-[5-Bromo-2-(3-fluoro-4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(3-fluoro-4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.
LC/MS t=4.18 min [MH^+] 538/540.

b) 3-{2-[5-Bromo-2-(3-fluoro-4-methoxy-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



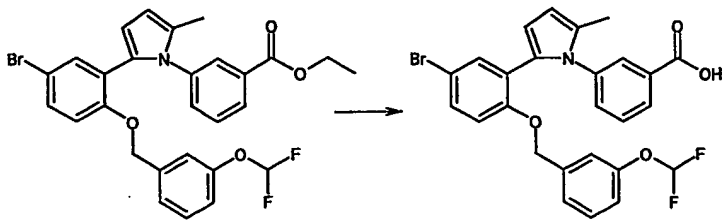
Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.
LC/MS t=4.01 [MH^+] 510/512.

Example 148 3-(2-{5-Bromo-2-[3-(1,1-difluoro-methoxy)-benzyloxy]-phenyl}-5-methyl-pyrrol- 1-yl)-benzoic acid

a) 3-(2-{5-Bromo-2-[3-(1,1-difluoro-methoxy)-benzyloxy]-phenyl}-5-methyl-pyrrol-1-yl)-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.
LC/MS t=4.21 min [MH^+] 556/568.

b) 3-(2-{5-Bromo-2-[3-(1,1-difluoro-methoxy)-benzyloxy]-phenyl}-5-methyl-pyrrol- 1-yl)-benzoic acid



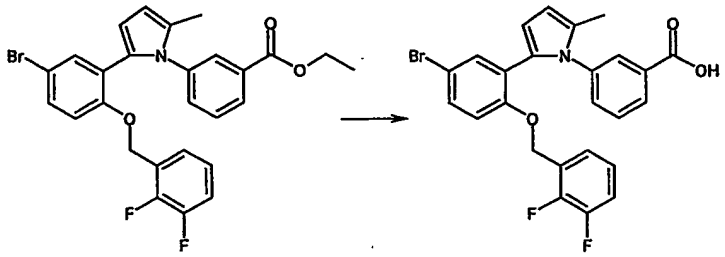
Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.
LC/MS t=4.04 min [MH^+] 528/530.

Example 149 3-{2-[5-Bromo-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.
LC/MS t=4.24 min [MH^+] 526/528.

b) 3-{2-[5-Bromo-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



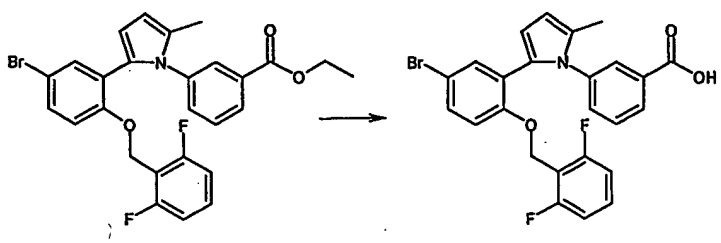
Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.
^{1}H-NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 4.79 (2H, s), 6.12 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.53 (1H, d, J=9Hz), 6.75 (1H, t, J=8Hz), 6.95-7.01 (1H, m), 7.03-7.09 (1H, m), 7.15-7.18 (1H, m), 7.21 (1H, dd, J=3Hz, 9Hz), 7.31 (1H, t, J=8Hz), 7.37 (1H, d, J=3Hz), 7.76 (1H, t, J=1Hz), 7.95 (1H, dt, J=1Hz, 8Hz).
LC/MS t=4.07 min [MH^+] 498/500.

Example 150 3-{2-[5-Bromo-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.
LC/MS t=4.17 min [MH^+] 526/528.

b) 3-{2-[5-Bromo-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.

^{1}H-NMR (400MHz, $CDCl_3$) 1.95 (3H, s), 4.78 (2H, s), 5.96 (1H, d, J=3Hz), 6.23 (1H, d, J=3Hz), 6.64 (1H, d, J=9Hz), 6.79 (2H, t, J=8Hz), 6.94-7.19 (5H, m), 7.73 (1H, t, J-1Hz), 7.75-7.80 (1H, m).

LC/MS [MH^+] 498/500.

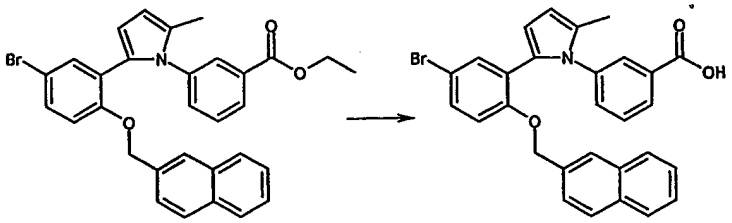
Example 151 3-{2-[5-Bromo-2-(naphthalen-2-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(naphthalen-2-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.

LC/MS t=4.40 [MH^+] 540/542.

b) 3-{2-[5-Bromo-2-(naphthalen-2-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.

LC/MS t=4.28 min [MH^+] 512/514.

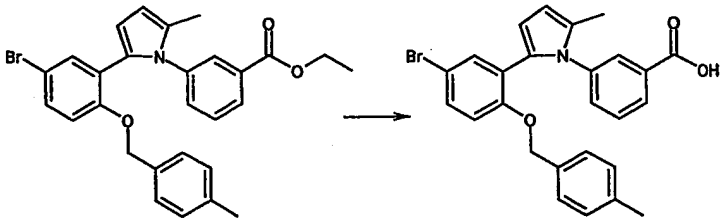
Example 152 3-{2-[5-Bromo-2-(4-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(4-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.

LC/MS t=4.31 min [MH^+] 504/506.

b) 3-{2-[5-Bromo-2-(4-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid using the appropriate benzyl bromide.

^{1}H-NMR (400MHz, $CDCl_3$) 2.14 (3H, s), 2.30 (3H, s), 4.69 (2H, s), 6.12 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.50 (1H, d, J=9Hz), 6.92 (2H, d, J=8Hz), 7.07 (2H, d, J=8Hz), 7.12-

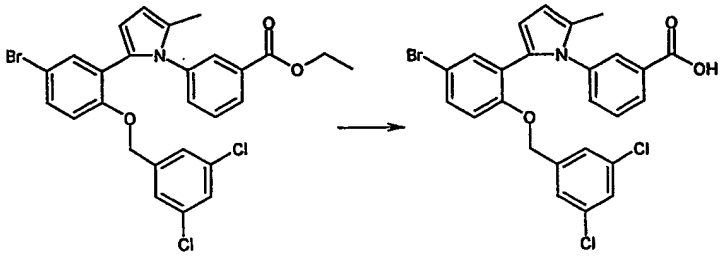
7.16 (2H, m), 7.28 (1H, t, J=8Hz), 7.34 (1H, d, J=3Hz), 7.78 (1H, t, J=1Hz), 7.93 (1H, dt, J=1Hz, 8Hz).
LC/MS = t=4.14 min [MH^+] 476/478.

Example 153 3-{2-[5-Bromo-2-(3,5-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(3,5-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.
LC/MS t=4.49 min [MH^+] 558/560.

b) 3-{2-[5-Bromo-2-(3,5-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



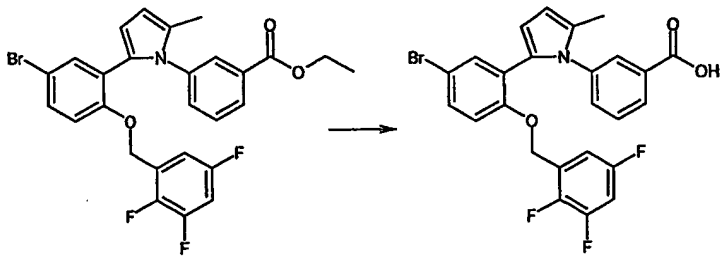
Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.
LC/MS t=4.39 min [MH^+] 530/532.

Example 154 3-{2-[5-Bromo-2-(2,3,5-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2,3,5-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.
LC/MS t=4.28 min [MH^+] 544/546.

b) 3-{2-[5-Bromo-2-(2,3,5-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid.
LC/MS t=4.10 min [MH^+] 516/518.

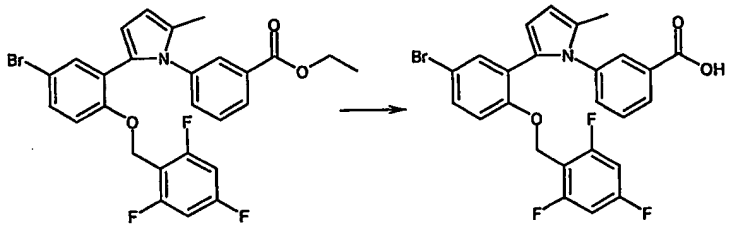
Example 155 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(biphenyl-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide.

LC/MS t=4.21 min [MH^+] 544/546.

b) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.06g) was dissolved in EtOH (1ml) and stirred with 2M NaOH (0.5ml) at reflux in a sealed vessel for 30 minutes. The solvent was removed in vacuo, the residue taken up in DCM and washed with dil. citric acid. The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached. The solvent was removed in vacuo and the residue freeze-dried in a MeCN/H_2O solution to yield a yellow solid (0.054g, 95%). ^{1}H-NMR (400MHz, $CDCl_3$) 2.14 (3H,s), 4.74 (2H, s), 6.08 (1H, d, J=3Hz), 6.24 (1H, d, J=3Hz), 6.66 (2H, t, J=8Hz), 6.72 (1H, d, J=9Hz), 7.14 (1H, m), 7.22-7.28 (2H, m), 7.34 (1H, t, J=8Hz), 7.78 (1H, t, J=1Hz), 7.99 (1H, dt, J=1Hz, J=8Hz).

LC/MS t=3.99 min [MH^+] 516/518.

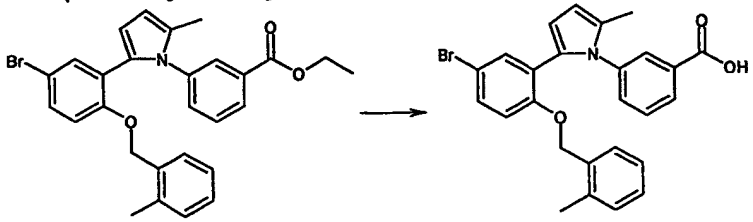
Example 156 3-{2-[5-Bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-[2-(5-Bromo-2-hydroxy-phenyl)-5-methyl-pyrrol-1-yl]-benzoic acid ethyl ester (0.15g, 0.375mmol), potassium carbonate (0.104g, 0.75mmol) and 2-methylbenzyl bromide (0.06ml, 0.413mmol) were stirred in DMF at 50°C for 2.5 hours under a nitrogen atmosphere. The reaction was diluted with EtOAc and washed with 2xH_2O and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant oil was then purified using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.

LC/MS t=4.34 min [MH^+] 504/506.

b) 3-{2-[5-Bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



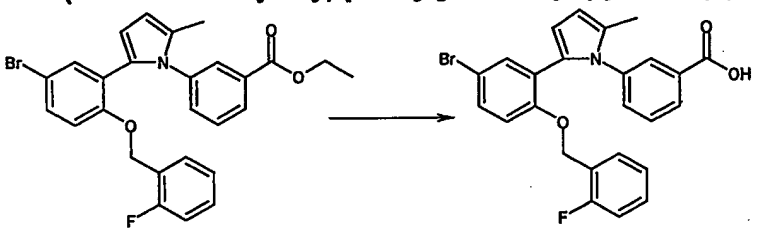
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.
LC/MS t=4.10 min [MH^+] 476/478.

Example 157 3-{2-[5-Bromo-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.
LC/MS t=4.27 min [MH^+] 508/510.

b) 3-{2-[5-Bromo-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



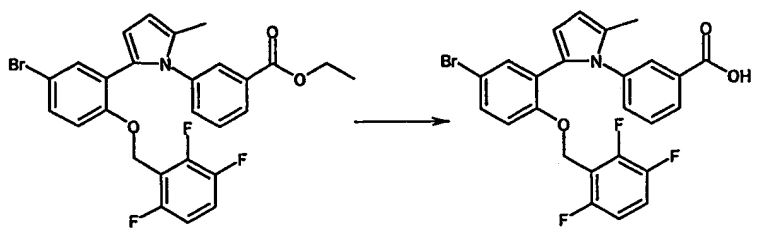
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.
^{1}H-NMR (400MHz, $CDCl_3$) 2.14 (3H, s), 4.79 (2H, s), 6.12 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.53 (1H, d, J=9Hz), 6.94-7.06 (3H, m), 7.12-7.24 (3H, m), 7.25-7.32 (1H+$CDCl_3$, m), 7.34 (1H, d, J=2Hz), 7.79 (1H, s), 7.94 (1H, d, J=7Hz).
LC/MS t=4.01 min [MH^+] 480/482.

Example 158 3-{2-[5-Bromo-2-(2,3,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2,3,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hexane.
LC/MS t=4.23 min [MH^+] 544/546.

b) 3-{2-[5-Bromo-2-(2,3,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.

^{1}H-NMR (400MHz, MeOD) 2.08 (3H, s), 4.83 (2H, s), 6.00 (1H, d, J=3Hz), 6.13 (1H, d, J=3Hz), 6.87 (1H, d, J=9Hz), 6.92-7.00 (1H, m), 7.09 (1H, d, J=8Hz), 7.22-7.37 (4H, m), 7.60 (1H, s), 7.89 (1H, d, J=8Hz).

LC/MS t=3.97 min [MH$^+$] 516/518.

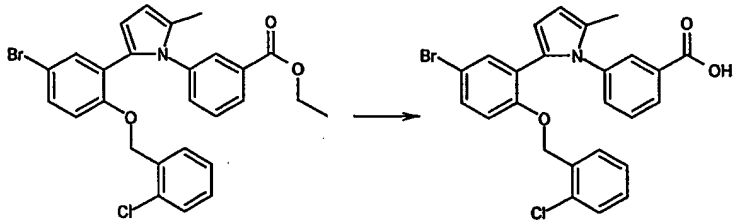
Example 159 3-{2-[5-Bromo-2-(2-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.

LC/MS t=4.18 min [MH$^+$] 524/526.

b) 3-{2-[5-Bromo-2-(2-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.

LC/MS t=4.17 min [MH$^+$] 496/498/500.

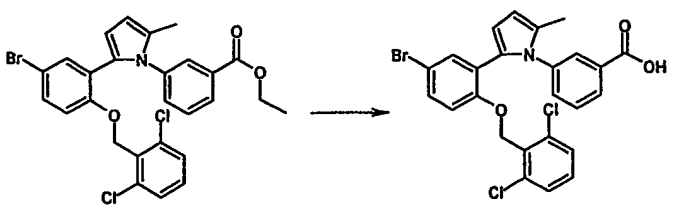
Example 160 3-{2-[5-Bromo-2-(2,6-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2,6-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 10% EtOAc/*i*-hex.

LC/MS t=4.18 min [MH$^+$] 558/560/562/564.

b) 3-{2-[5-Bromo-2-(2,6-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



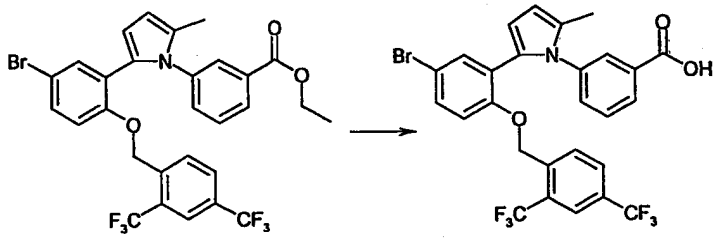
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.
LC/MS t=4.16 min [MH^+] 530/532/534/536.

Example 161 3-{2-[5-Bromo-2-(2,4-bis-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2,4-bis-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 10% EtOAc/*i*-hex.
LC/MS t=4.53 min [MH^+] 626/628.

b) 3-{2-[5-Bromo-2-(2,4-bis-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



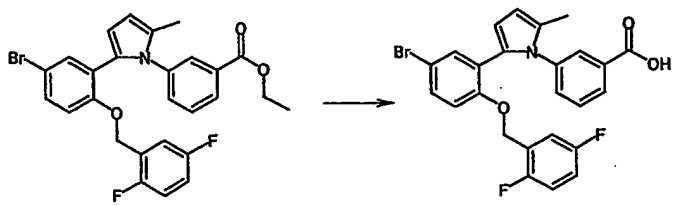
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.
LC/MS t=4.29 min [MH^+] 598/600.

Example 162 3-{2-[5-Bromo-2-(2,5-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2,5-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 10% EtOAc/*i*-hex.
LC/MS t=4.28 min [MH^+] 526/528.

b) 3-{2-[5-Bromo-2-(2,5-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.

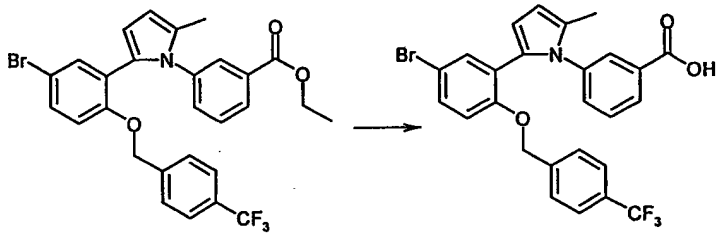
^{1}H-NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.77 (2H, s), 6.15 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.52 (1H, d, J=9Hz), 6.64-6.70 (1H, m), 6.86-6.99 (2H, m), 7.17-7.24 (2H, m), 7.33 (1H, t, J=8Hz), 7.39 (1H, d, J=2Hz), 7.81 (1H, s), 7.97 (1H, d, J=8Hz).
LC/MS t=4.03 min [MH^+] 498/500.

Example 163 3-{2-[5-Bromo-2-(4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 10% EtOAc/*i*-hex.
LC/MS t=4.38 min [MH^+] 558/560.

b) 3-{2-[5-Bromo-2-(4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



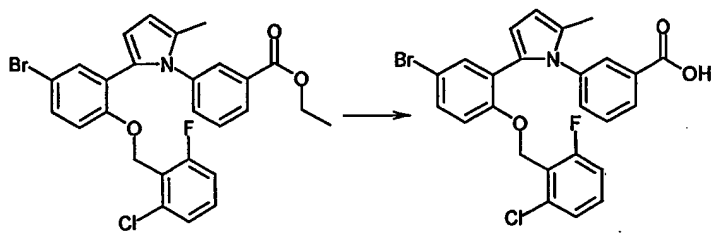
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid, however further purification was required on the MDAP.
LC/MS t=4.15 min [MH^+] 530/532.

Example 164 3-{2-[5-Bromo-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.
LC/MS t=4.30 min [MH^+] 542/544/546.

b) 3-{2-[5-Bromo-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



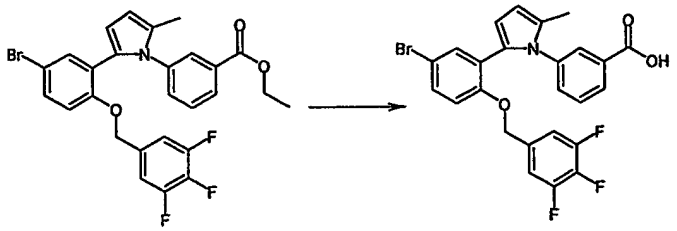
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.
LC/MS t=4.06 min [MH^+] 514/516/518.

Example 165 3-{2-[5-Bromo-2-(3,4,5-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(3,4,5-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.
LC/MS t=4.35 min [MH^+] 544/546.

b) 3-{2-[5-Bromo-2-(3,4,5-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



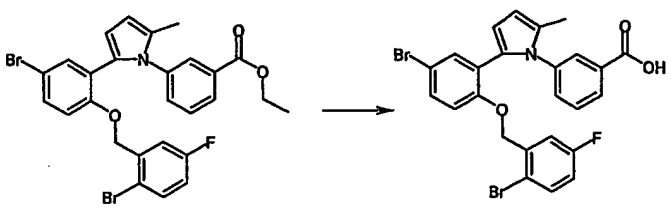
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.
LC/MS t=4.12 min [MH^+] 516/518.

Example 166 3-{2-[5-Bromo-2-(2-bromo-5-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2-bromo-5-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.
LC/MS t=4.45 min [MH^+] 586/588/590.

b) 3-{2-[5-Bromo-2-(2-bromo-5-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



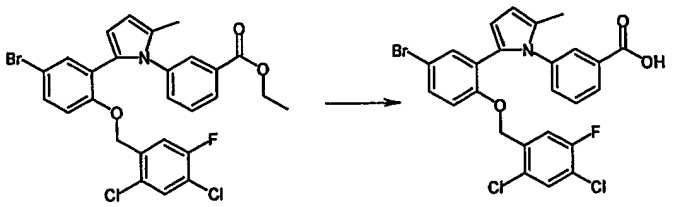
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.
LC/MS t=4.25 min [MH^+] 558/560/562.

Example 167 3-{2-[5-Bromo-2-(2,4-dichloro-5-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2,4-dichloro-5-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.
LC/MS t=4.34 min

b) 3-{2-[5-Bromo-2-(2,4-dichloro-5-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



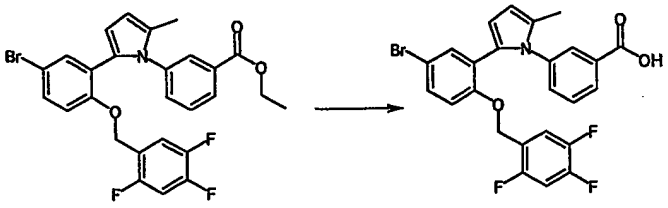
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.
LC/MS t=4.16 min 548/550/552.

Example 168 3-{2-[5-Bromo-2-(2,4,5-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2,4,5-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.
LC/MS t=4.11 min [MH^+] 544/546.

b) 3-{2-[5-Bromo-2-(2,4,5-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.

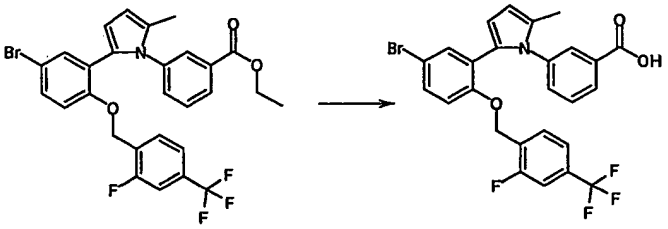
^{1}H-NMR (400MHz, $CDCl_3$) 1.98 (3H, s), 4.68 (2H, s), 5.45-5.80 (1H, broad s), 6.03 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.42 (1H, d, J=9Hz), 6.70-6.86 (2H, m), 6.93-7.05 (3H, m), 7.21 (1H, d, J=2Hz), 7.72-7.75 (2H, m).
LC/MS t=3.90 min [MH^+] 516/518.

Example 169 3-{2-[5-Bromo-2-(2-fluoro-4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2-fluoro-4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.
LC/MS t=4.19 min [MH^+] 576/578.

b) 3-{2-[5-Bromo-2-(2-fluoro-4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



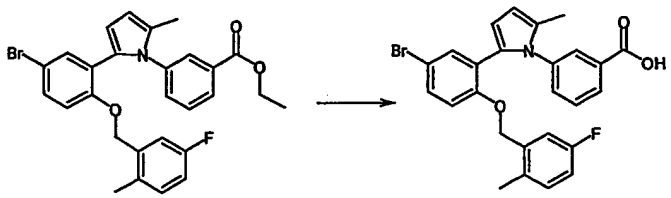
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.
LC/MS t=3.96 min [MH^+] 548/550.

Example 170 3-{2-[5-Bromo-2-(5-fluoro-2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(5-fluoro-2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.
LC/MS t=4.34 min [MH^+] 522/524.

b) 3-{2-[5-Bromo-2-(5-fluoro-2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



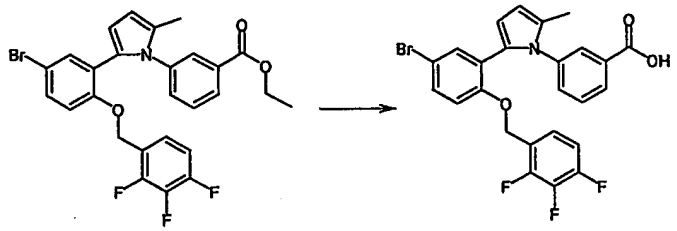
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.
LC/MS t=4.11 min [MH^+] 494/496.

Example 171 3-{2-[5-Bromo-2-(2,3,4-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2,3,4-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.
LC/MS t=4.31 min [MH^+] 544/546.

b) 3-{2-[5-Bromo-2-(2,3,4-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



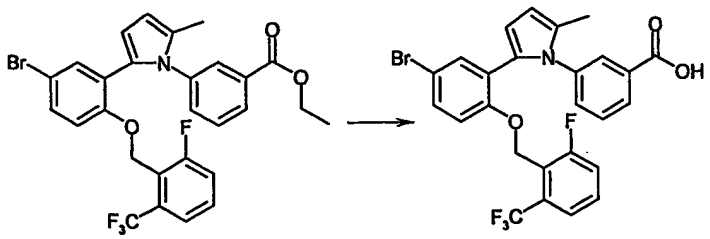
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.
LC/MS t=4.07 min [MH^+] 514/516.

Example 172 3-{2-[5-Bromo-2-(2-fluoro-6-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2-fluoro-6-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.
LC/MS t=4.29 min [MH^+] 576/578.

b) 3-{2-[5-Bromo-2-(2-fluoro-6-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



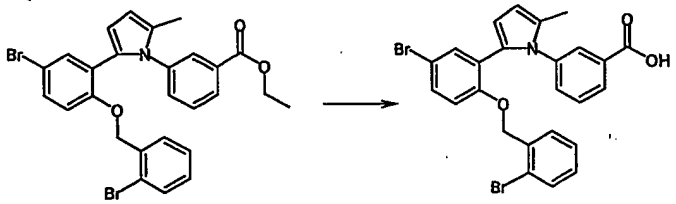
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.
LC/MS t=4.04 min [MH^+] 548/550.

Example 173 3-{2-[5-Bromo-2-(2-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.
LC/MS t=4.29 min

b) 3-{2-[5-Bromo-2-(2-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



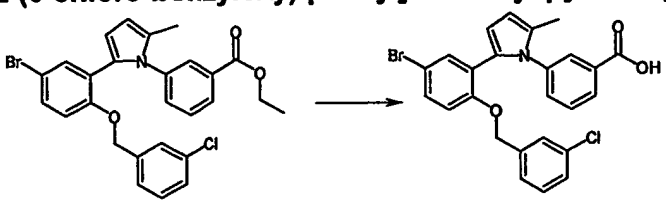
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid, however further purification was required using column chromatography on the Biotage® Horizon system on a 25S reverse phase column eluting in a gradient of 30-100% MeCN/H_2O.
LC/MS t=4.01 min [MH^+] 540/542/544.

Example 174 3-{2-[5-Bromo-2-(3-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(3-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (20g) eluting in 20% EtOAc/*i*-hex.
LC/MS t=4.39 min

b) 3-{2-[5-Bromo-2-(3-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.

LC/MS t=4.18 min [MH^+] 496/498.

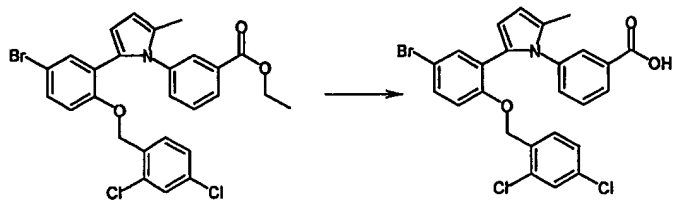
Example 175 3-{2-[5-Bromo-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester using the appropriate benzyl bromide, however purification achieved using column chromatography on a SPE cartridge (25g) eluting in 20% EtOAc/*i*-hex.

LC/MS t=4.54 min [MH^+] 558/560/562.

b) 3-{2-[5-Bromo-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



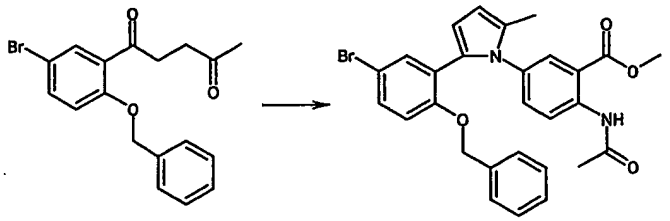
Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid, however further purification was required using the MDAP.

^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.74 (2H, s), 6.15 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.48 (1H, d, J=9Hz), 6.90 (1H, d, J=8Hz), 7.15 (1H, dd, J=2Hz, 8Hz), 7.18-7.23 (2H, m), 7.32 (1H, d, J=2Hz), 7.35 (1H, t, J=8Hz), 7.40 (1H, d, J=2Hz), 7.78-7.81 (1H, m), 7.99 (1H, d, J=8Hz).

LC/MS t=4.37 min [MH^+] 530/532/534.

Example 176 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid

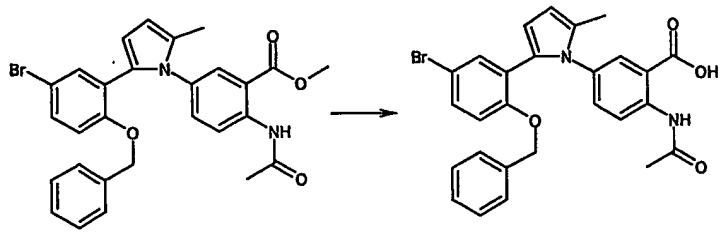
a) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester



1-(2-Benzyloxy-5-bromo-phenyl)-pentane-1,4-dione (0.10g, 0.277mmol), 6-acetylamino-3-amino-benzoic acid methyl ester (0.063g, 0.305mmol) and *p*-TSA (cat.) in NMP (2ml) were heated in a sealed vessel at 150°C for 10 miuntes using microwaves. Upon cooling the reaction was diluted with Et_2O and washed with dil. citric acid. The organic layer was extracted and the aqueous layer washed with 3xEt_2O, the combined organic extracts were then washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The

residue was purified by chromatography on silica gel eluting in 20% EtOAc/*i*-hex. This yielded a white solid (0.112g, 60%).
LC/MS t=4.11 min [MH^+] 533/535.

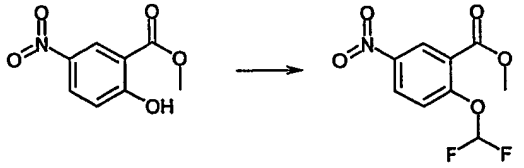
b) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid



3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid ethyl ester (0.112g) was dissolved in MeOH (2ml) and heated with 2N NaOH (1ml) in a sealed vessel at 100°C for 30 minutes. Upon cooling the reaction was diluted with EtOAc and washed with dil. citric acid and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound as a yellow solid (0.075g, 69%).
^{1}H-NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 2.23 (3H, s), 4.77 (2H, s), 6.12 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.53 (1H, d, J=9Hz), 7.05-7.09 (2H, m), 7.16 (1H, dd, J=2Hz, 9Hz), 7.20 (1H, dd, J=2Hz, 9Hz). 7.25-7.29 (3H+$CDCl_3$, m), 7.40 (1H, d, J=2Hz), 7.74 (1H, d, J=2Hz), 8.60 (1H, d, J=9Hz), 10.90 (1H, s).
LC/MS t=4.30 min [MH^+] 519/521.

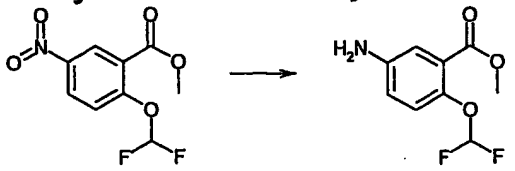
<u>Example 177 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-(1,1-difluoro-methoxy)-benzoic acid</u>

a) 2-Difluoromethoxy-5-nitro-benzoic acid methyl ester



Methyl-5-nitrosalicylate (ex Pfaltz and Bauer) (4.792g), sodium chlorodifluoroacetate (4.444g) and sodium carbonate (3.147g) were heated at 100°C in DMF (97mL) for 2.5 hours. Upon cooling, the mixture was partitioned between Et_2O and water. The layers were separated and the aqueous phase was extracted further with Et_2O. The combined extracts were dried (Na_2SO_4), filtered and evaporated to give the title compound, which was used without further purification.
^{1}H NMR (400MHz, $CDCl_3$) 3.98 (3H, s), 6.72 (1H, t, J=73Hz), 7.45 (1H, d, J=9Hz), 8.42 (1H, dd, J=3Hz, J=9Hz), 8.76 (1H, d, J=3Hz).

b) 5-Amino-2-difluoromethoxy-benzoic acid methyl ester

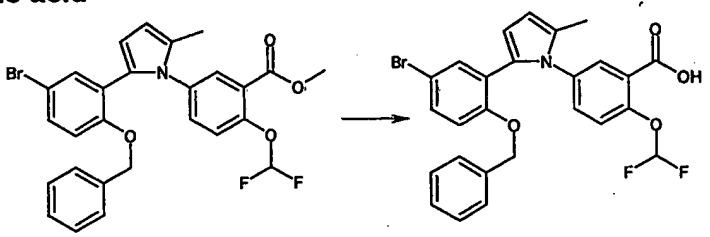


2-Difluoromethoxy-5-nitro-benzoic acid methyl ester (2.5g,10 mmol) was hydrogenated at atmospheric temperature and pressure in methanol (50ml) with palladium on charcoal 5% wet (0.4g) for six hours. The reaction mixture was then filtered through high-flo and evaporated down to an oil which turned into a solid to give the tile compound (2.15g,99%).
LC/MS t=2.51min [MH^+] 218, [MH^-] 216

c) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-(1,1-difluoro-methoxy)-benzoic acid methyl ester

Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however purification achieved using column chromatography on the Biotage QUAD 4 system on a 25S column eluting in 10% EtOAc/*i*-hex.
LC/MS t=4.19 [MH^+] 542/544.

d) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-(1,1-difluoro-methoxy)-benzoic acid



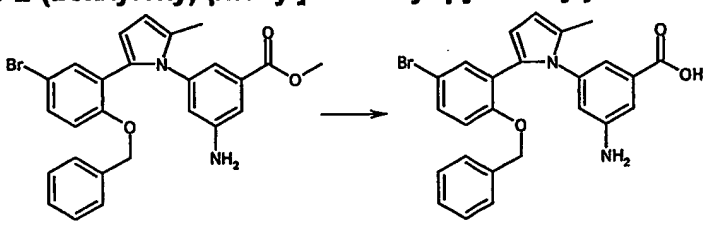
Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid.
^{1}H-NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 4.72 (2H, s), 6.13 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.55 (1H, d, J=9Hz), 6.59 (1H, t, J=75Hz), 7.03-7.10 (4H, m), 7.22 (1H, dd, J=3Hz, 9Hz), 7.25-7.31 (3H+$CDCl_3$, m), 7.40 (1H, d, J=3Hz), 7.68 (1H, d, J=2Hz).
LC/MS t=4.14 [MH^+] 528/530.

<u>Example 178 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid</u>

a) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester

Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however purification achieved using column chromatography on the Biotage QUAD 4 system on a 25S column eluting in 20% EtOAc/*i*-hex.
LC/MS t=3.68 min [MH^+] 491/493.

b) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid.

^{1}H-NMR (400MHz, MeOD) 2.12 (3H, s), 4.86 (2H, s), 5.99-6.02 (1H, m), 6.19-6.22 (1H, m), 6.44-6.46 (1H, m), 6.68-6.72 (1H, m), 7.02-7.05 (1H, m), 7.12-7.32 (8H, m).

LC/MS t=3.58 min [MH$^+$] 477/479.

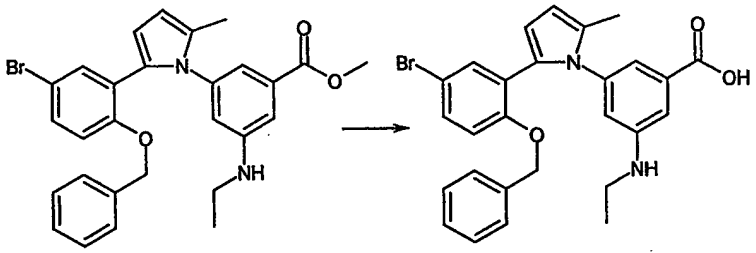
Example 179 3-[2-(5-Bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-ethylamino-benzoic acid

a) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-ethylamino-benzoic acid methyl ester

3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester (0.25g, 0.509mmol), potassium carbonate (0.01g, 0.509mmol), ethyl iodide (0.04ml, 0.509mmol) and NMP (3ml) were heated in a sealed vessel using microwaves for 30 minutes. Upon cooling the reaction was diluted with Et_2O and washed with dilute citric acid, the orgaincs were extracted and the aqueous washed with 2xEt_2O. The combined organics were then washed with 2xH_2O and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with 10% EtOAc/iso-hexane. This yielded the title compound as a clear oil (0.036g, 14%).

LC/MS t=4.16 min [MH$^+$] 519/521.

b) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-ethylamino-benzoic acid



Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid.

LC/MS t=3.79 min [MH$^+$] 505/507.

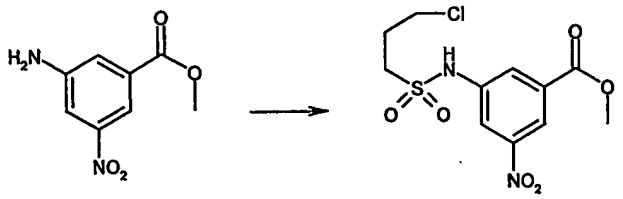
Example 180 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid

a) 3-Amino-5-nitro-benzoic acid methyl ester

To a solution of 3-amino-5-nitro-benzoic acid (ex Avocado) (65 g, 357 mmol, 1 equiv) in MeOH (650 ml) at 0°C was added $SOCl_2$ dropwise (39 ml, 536 mmol, 1.5 equiv). The resulting solution was allowed to warm to room temperature and stirred for 16 h. A further portion of $SOCl_2$ (10 ml, 137 mmol, 0.4 equiv) was added dropwise and the solution was stirred at room temperature for 5 h, at 50°C for 2 h and then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in EtOAc and the organic phase washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*.

The solid residue was triturated with EtOAc/*iso*-hexane to give the title compound (55 g, 78%).

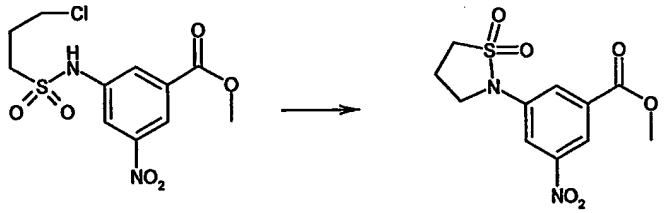
b) 3-(3-Chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester



To a solution of 3-amino-5-nitro-benzoic acid methyl ester (45 g, 229 mmol, 1 equiv) in CH_2Cl_2 (450 ml) was added pyridine (18.5 ml, 229 mmol, 1 equiv), DMAP (100 mg, 0.8 mmol, catalytic) and 3-chloropropanesulfonyl chloride (28 ml, 230 mmol). The resulting mixture was stirred for 40 h then diluted with EtOAc. The organic phase was diluted with 2MN HCl. The resulting solid was filtered to give 3-(3-chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (23 g, 32%). The filtrate was separated and the organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with EtOAc and *iso*-hexane to give a further 50 g (65%) of 3-(3-chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester, as a pale brown solid, which was used in the next step without further purification.

LC/MS t = 3.11 min, [MH] = 335.

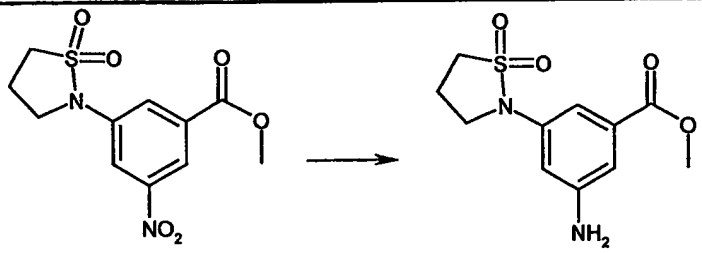
c) 3-(1,1-Dioxo-1λ^6-*iso*thiazolidin-2-yl)-5-nitro-benzoic acid methyl ester



To a solution of 3-(3-chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (73g, 217 mmol, 1 equiv) in EtOH (600 ml) was added Et_3N (60 ml, 430 mmol, 2 equiv) and the resulting mixture was refluxed for 3 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with 2M HCl, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane and EtOAc to give 3-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (58 g, 88%), as a pale brown solid, which was used in the next step without further purification.

LC/MS t = 2.78 min $[M+H+NH_3^+]$ = 318.0

d) 3-Amino-5-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-benzoic acid methyl ester



A flask was charged with 3-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (25 g, 83 mmol, 1 equiv) and 10% palladium (0) on charcoal (50% wet, 5 g, 10% w/w) and EtOH (500 ml). The resulting suspension was stirred under an atmosphere of hydrogen (atmospheric pressure) for 4 h after which time the catalyst was filtered off, through a pad of celite. The catalyst was washed three times with DMF and the combined organic layers were concentrated *in vacuo*. The residue was dissolved in EtOAc and filtered again through celite in order to remove residual catalyst. The organic phase was concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-amino-5-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-benzoic acid methyl ester (18 g, 80%), as a pale brown solid, which was used in the next step without further purification.

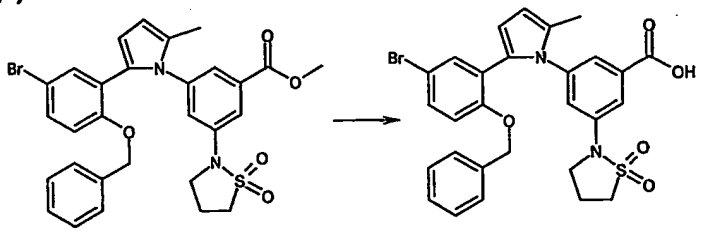
LC/MS t = 2.16 min [MH^+] = 271

e) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester

Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl)-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester, however purification achieved using column chromatography on the Biotage® QUAD 4 system on a 25S column eluting in 50% EtOAc/*i*-hex.

LC/MS t=3.71 min [MH^+] 595/597.

f) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid.

^{1}H-NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 2.45 (2H, m), 3.33 (2H, t, J=7Hz), 3.43 (2H, t, J=7Hz), 4.75 (2H, s), 6.13 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.53 (1H, d, J=9Hz), 7.04 (2H, dd, J=1Hz, 8Hz), 7.10 (1H, t, J=2Hz), 7.20 (1H, dd, J=2Hz, 9Hz), 7.22-7.30 (3H+$CDCl_3$, m), 7.43 (1H, d, J=2Hz), 7.49 (1H, t, J=1Hz), 7.77-7.79 (1H, m).

LC/MS t=3.82 min [MH^+] 581/583.

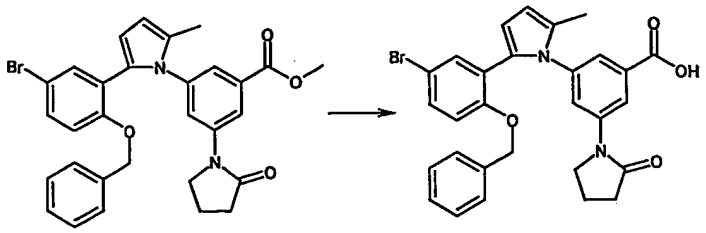
Example 181 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid

a) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester

Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however purification achieved using column chromatography on the Biotage® QUAD 4 system on a 25S column eluting in 50% EtOAc/*i*-hex.

LC/MS t=3.75 min [MH^+] 559/561.

b) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid.

^{1}H-NMR (400MHz, $CDCl_3$) 2.10 (2H, m), 2.20 (3H, s), 2.55 (2H, t, J=8Hz), 3.52 (2H, m), 4.76 (2H, s), 6.13 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.52 (1H, d, J=9Hz), 7.00-7.03 (2H, m), 7.19 (1H, dd, J=2Hz, 9Hz), 7.25-7.29 (3H+$CDCl_3$, m), 7.42 (1H, d, J=3Hz), 7.48-7.50 (1H, m), 7.56 (1H, t, J=2Hz), 8.19-8.21 (1H, m).

LC/MS t=3.88 min [MH^+] 545/547.

Example 182 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid

a) 3-Amino-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester

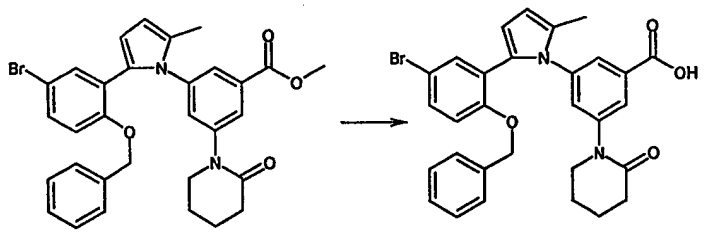
Prepared in an analogous manner to 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester using the appropriate amine.

b) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester

Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however purification achieved using column chromatography on the Biotage® QUAD 4 system on a 25S column eluting in 50% EtOAc/*i*-hex.

LC/MS t=3.94 min [MH^+] 573/575.

c) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid.

^{1}H-NMR (400MHz, $CDCl_3$) 1.45-1.91 (4H, m), 2.15-2.22 (3H, m), 2.33-2.54 (2H, m), 2.89-3.33 (2H, m), 4.71-4.78 (2H, m), 6.09-6.14 (1H, m), 6.28-6.34 (1H, m), 6.51-6.55 (1H, m), 7.02-7.30 (7H, m), 7.36-7.41 (1H, m), 7.59 (1H, t, J=1Hz), 7.87 (1H, t, J=1Hz).

LC/MS t=3.61 min.

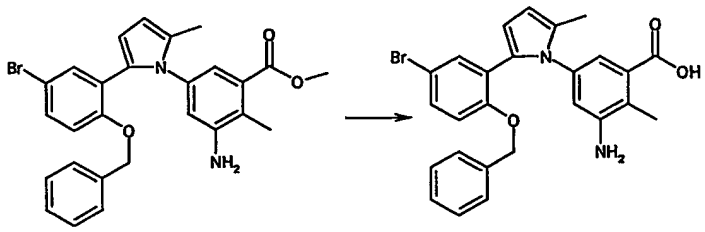
Example 183 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid

a) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid methyl ester

Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however purification achieved by column chromatography on the Biotage® QUAD 4 system on a 25S column eluting in 20% EtOAc/*i*-hex.

LC/MS t=3.75 min [MH^+] 505/507.

b) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid.

^{1}H-NMR (400MHz, $CDCl_3$) 2.14 (3H,s), 2.37 (3H, s), 4.80 (2H, s), 6.09 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.41 (1H, d, J=2Hz), 6.45 (1H, d, J=9Hz), 7.07-7.11 (3H, m), 7.17 (1H, dd, J=2Hz, 9Hz), 7.25-7.32 (4H, m), 7.37 (1H, d, J=2Hz).

LC/MS t=3.79 min [MH^+] 491/493.

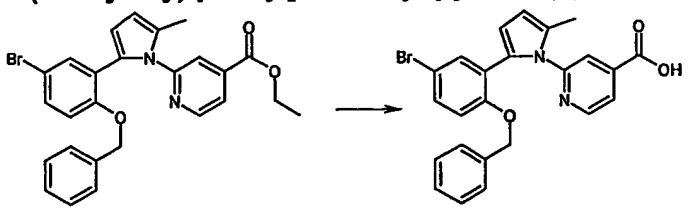
Example 184 2-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid

a) 2-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid ethyl ester

Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however purification achieved by column chromatography on a Biotage® 25M column eluting in 20% EtOAc/*i*-hex.

LC/MS t=4.11 min [MH^+] 491/493.

b) 2-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isonicotinic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid.

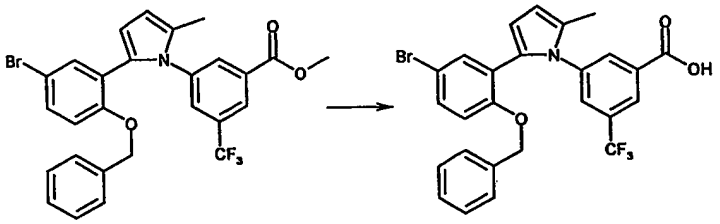
LC/MS t=3.74 min [MH^+] 463/465.

Example 185 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid

a) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester

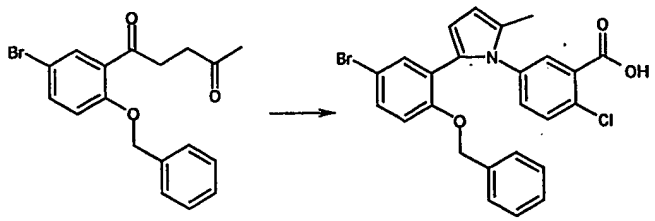
Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however purification achieved using column chromatography on a Biotage® 25S column eluting in 5% EtOAc/*i*-hex.
LC/MS t=4.40 min [MH^+] 544/546.

b) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid



3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid ethyl ester (0.06g) was dissolved in EtOH (2ml) and stirred with 2N NaOH (1ml) at 120°C in a sealed vessel for 3 minutes using microwaves. The solvent was removed in vacuo, the residue taken up in DCM and washed with dil. citric acid. The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached. The solvent was removed in vacuo and the residue freeze-dried in a $MeCN/H_2O$ solution to yield a yellow solid (0.049g, 86%).
^{1}H-NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.69 (2H, s), 6.17 (1H, d, J=3Hz), 6.32 (1H, d, J=4Hz), 6.52 (1H, d, J=9Hz), 6.98-7.03 (2H, m), 7.22 (1H, dd, J=3Hz, 9Hz), 7.23-7.31 (3H+$CDCl_3$, m), 7.41-7.45 (2H, m), 7.86-7.88 (1H, m), 8.17 (1H, s).
LC/MS t=4.05 min [MH^+] 530/532.

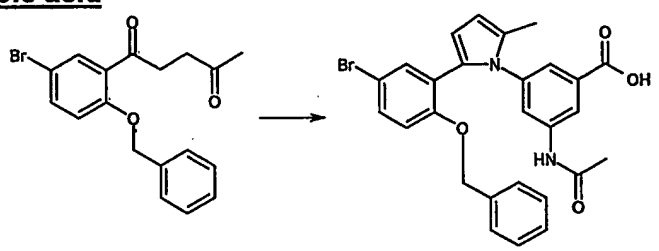
Example 186 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid



1-[2-(Benzyloxy)-5-bromo-phenyl]-pentane-1,4-dione (0.12g, 0.322mmol), 5-amino-2-chloro-benzoic acid (0.062g, 0.365mmol) and *p*-TSA (cat.) in NMP (2ml) were heated in a sealed vessel at 150°C for 10 miuntes using microwaves. Upon cooling the reaction was diluted with Et_2O and washed with dil. citric acid. The organic layer was extracted and the aqueous layer washed with 3xEt_2O, the combined organic extracts were then washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by MDAP. This yielded the title compound as a white solid (0.04g, 24%).

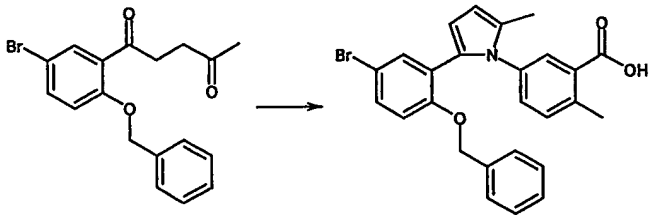
^{1}H-NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 4.72 (2H, s), 6.14 (1H, dd, J=1Hz, 3Hz), 6.29 (1H, d, J=3Hz), 6.54 (1H, d, J=9Hz), 6.97-7.03 (3H, m), 7.21-7.31 (5H, m), 7.44 (1H, d, J=3Hz), 7.65 (1H, d, J=3Hz).
LC/MS t=4.32 min [MH^+] 496/498.

Example 187 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-acetylamino-benzoic acid



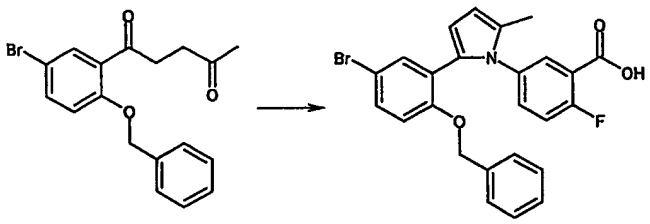
Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, however purification achieved using column chromatography on a SPE cartridge (25g) eluting in 5% MeOH/DCM.
^{1}H-NMR (400MHz, MeOD) 2.07 (3H, s), 2.13 (3H, s), 4.78 (2H, s), 6.06 (1H, d, J=3Hz), 6.21 (1H, d, J=3Hz), 6.65 (1H, d, J=9Hz), 7.09 (2H, d, J=7Hz), 7.18 (1H, dd, J=2Hz, 9Hz), 7.22-7.31 (4H, m), 7.35 (1H, s), 7.51 (1H, s), 8.02 (1H, s).
LC/MS t=3.71 min [MH^+] 517/519.

Example 188 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, however purification achieved using column chromatography on a SPE cartridge (25g) eluting in 20% EtOAc/*i*-hex.
^{1}H-NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 2.62 (3H, s), 4.77 (2H, s), 6.12 (1H, d, J=3Hz), 6.30 (1H, d, J=2Hz), 6.52 (1H, d, J=9Hz), 7.00-7.04 (3H, m), 7.11 (1H, d, J=8Hz), 7.18 (1H, dd, J=2Hz, 9Hz), 7.22-7.29 (3H+$CDCl_3$, m), 7.38 (1H, d, J=3Hz), 7.77 (1H, d, J=2Hz).
LC/MS t=4.11 min [MH^+] 476/478.

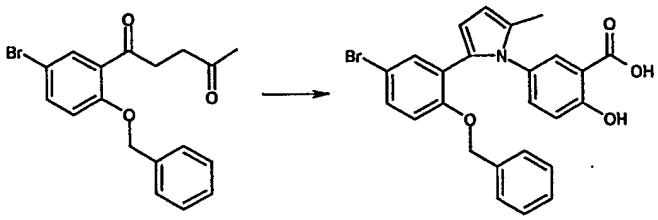
Example 189 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, however purification achieved using column chromatography on a SPE cartridge (10g) eluting in 20% EtOAc/*i*-hex.

^{1}H-NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 4.75 (2H, s), 6.12 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.55 (1H, d, J=9Hz), 6.95-7.01 (1H, m), 7.04-7.12 (3H, m), 7.22 (1H, dd, J=3Hz, 9Hz), 7.25-7.32 (3H+$CDCl_3$, m), 7.40 (1H, d, J=3Hz), 7.68 (1H, dd, J=3Hz, 7Hz).
LC/MS t=4.00 min [MH^+] 480/482.

Example 190 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, however purification achieved using the MDAP.

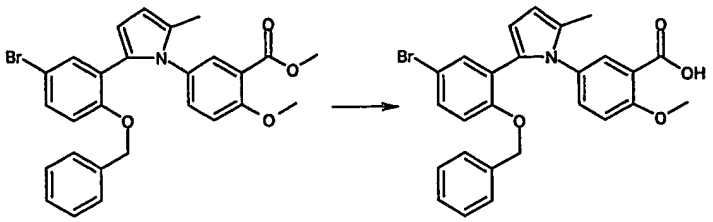
^{1}H-NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 4.80 (2H, s), 6.11 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.54 (1H, d, J=9Hz), 6.83 (1H, d, J=9Hz), 7.05-7.10 (3H, m), 7.19 (1H, d, J=3Hz, 9Hz), 7.25-7.32 (3H+$CDCl_3$, m), 7.37 (1H, d, J=2Hz), 7.56 (1H, d, J=2Hz), 10.51 (1H, broad s).
LC/MS t=4.28 min [MH^+] 478/480.

Example 191 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methoxy-benzoic acid

a) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methoxy-benzoic acid methyl ester

3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid (0.069g, 0.144mmol), sodium hydride (0.048g, 2mmol) in anhydrous DMF were stirred at 0°C for 2 hours, methyl iodide (0.1ml, 1.44mmol) was added and the mixture was stirred under a nitrogen atmosphere for 3 hours. The solvent was removed *in vacuo* and the residue taken up in EtOAc and washed with 2xH_2O and brine. The organics were then dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by column chromatography, using a SPE cartridge (10g) eluting with 20% EtOAc/*iso*-hexane. This yielded the title compound as a clear oil (0.037g, 52%).
LC/MS t=3.81 min [MH^+] 506/508.

b) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methoxy-benzoic acid

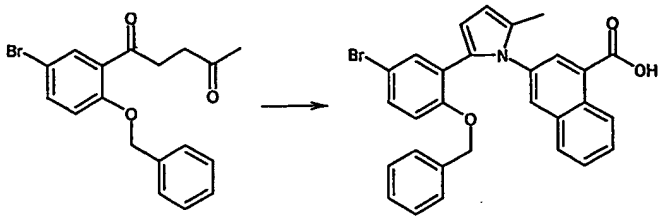


Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid.

^{1}H-NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 4.04 (3H, s), 4.83 (2H, s), 6.11 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.55 (1H, d, J=9Hz), 6.88 (1H, d, J=9Hz), 7.06-7.09 (2H, m), 7.12-7.18 (2H, m), 7.25-7.32 (4H+$CDCl_3$, m), 7.97 (1H, d, J=3Hz).

LC/MS t=3.65 min [MH^+] 492/494.

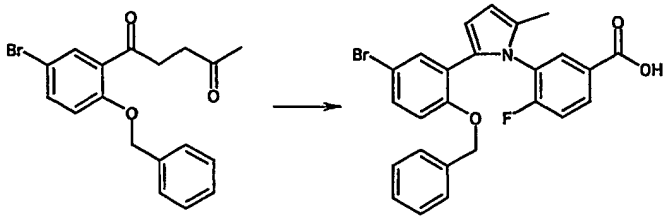
Example 192 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-1-naphthoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, however purification achieved by column chromatography using a SPE cartridge (10g) eluting in 30% EtOAc/*i*-hex.

LC/MS t=3.95 min [MH^+] 512/514.

Example 193 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-4-fluoro-benzoic acid

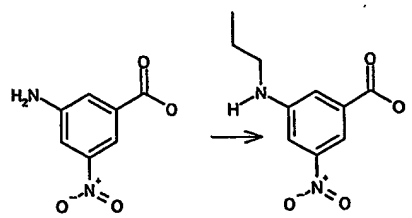


Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, however purification achieved by column chromatography on a Biotage® 15M column eluting in 30% EtOAc/*i*-hex.

LC/MS t=3.79 min [MH^+] 480/482.

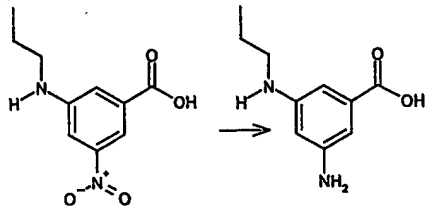
Example 194 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-propylamino-benzoic acid

a) 3-Nitro-5-(propylamino) benzoic acid



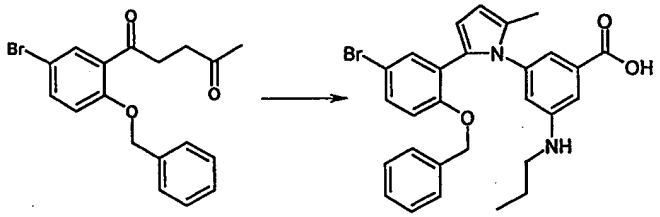
3-Amino-5-nitrobenzoic acid(500mg,2.7mmol) in 2-butanone (2ml) with potassium carbonate (500mg) was treated with 1-bromopropane (1ml,exess).
The reaction mixture was then heated under reflux, under nitrogen for three hours, filtered and the residue washed with EtOAc (10ml).The organic layer was then washed with water (2x10ml), dried over magnesium sulphate, and chromatographed on a Water's sep-pack(10g) giving the title compound (350mg,58%).
LC/MS t=3.23 min

b) 3-Amino-5-(propylamino)benzoic acid



3-Nitro-5-(propylamino) benzoic acid (350mg,1.5mmol) in methanol (15ml) and palladium on charcoal 5% wet, was hydrogenated at atmospheric temperature and pressure for 4 hours. The reaction mixture was then filtered through high-flo and evaporated down to give the title compound (290mg,100%).
LC/MS t=2.14min [MH^+] 195

c) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-propylamino-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however further purification was achieved using the MDAP.
LC/MS t=3.91 min [MH^+] 519/521.

<u>Example 195 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-(1,1-difluoro-methoxy)-benzoic acid</u>

a) 5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-benzaldehyde

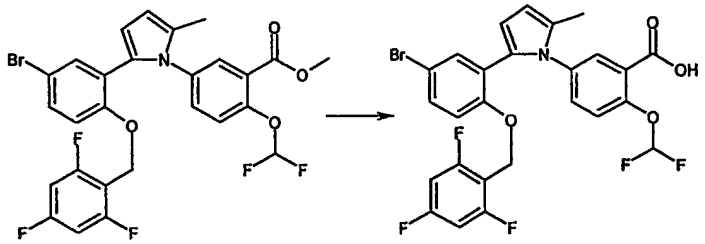
5-Bromo-2-hydroxy-benzaldehyde (4g, 19.8mmol), 2,4,6-trifluoro-benzyl bromide (5g, 21.9mmol) and potassium carbonate (5.5g, 39.8mmol) were stirred in DMF (75ml) at 55°C under a nitrogen atmosphere overnight. Upon cooling the reaction mixture was diluted with EtOAc and washed with H_2O. The organic layer was extracted and the aqueous layer

washed with 3xEtOAc. The combined organic extracts were then washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound as a white solid (6.95g, 100%).
LC/MS t=3.50 min.

b) 1-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-pentane-1,4-dione
2-(2,4,6-Trifluoro-benzyloxy)-5-bromo-benzaldehyde (6.95g, 20.15mmol), triethylamine (8.4ml, 60.43mmol), methyl vinyl ketone (1.71ml, 20.55mmol) and 3-ethyl-5-(2-hydroxyethyl)-4-ethylthiazolium bromide (1.52g, 6.04mmol) were stirred at refluxed in EtOH (15ml) under a nitrogen atmosphere for 21 hours. Upon cooling the reaction mixture was diluted with EtOAc and washed with saturated NH_4Cl. The organic layer was extracted and the aqueous layer washed with 3xEtOAc. The combined organic extracts were then washed with saturated $NaHCO_3$ and brine and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with 20% EtOAc/iso-hexane. This yielded the title compound as an off white solid (5.77g, 70%).
LC/MS t=3.58 min [MH^+] 415/417.

c) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-(1,1-difluoro-methoxy)-benzoic acid methyl ester
Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however purification achieved using column chromatography on the Biotage® Horizon system on a 25S column eluting in a gradient of 5-20% EtOAc/*i*-hex.
LC/MS t=4.09 min [MH^+] 596/598.

d) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-(1,1-difluoro-methoxy)-benzoic acid



Procedure as for 3-[2-(5-bromo-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-5-trifluoromethyl-benzoic acid, however further purification was required using column chromatography on the Biotage® Horizon system on a 25S reverse phase column eluting in a gradient of 30-100% MeCN/H_2O.
^{1}H-NMR (400MHz, $CDCl_3$) 2.14 (3H, s), 4.73 (2H, s), 6.07 (1H, d, J=3Hz), 6.21 (1H, d, J=3Hz), 6.59 (1H, t, J=75Hz), 6.62-6.69 (2H, m), 6.74 (1H, d, J=9Hz), 7.08-7.16 (2H, m), 7.25-7.32 (2H+$CDCl_3$, m), 7.71 (1H, d, J=2Hz).
LC/MS t=3.79 min [MH^+] 582/584.

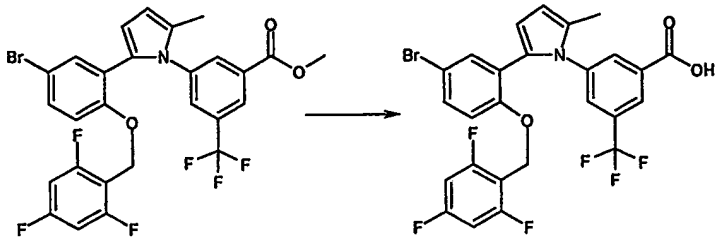
<u>Example 196 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid</u>

a) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-trifluoromethyl-benzoic acid methyl ester.

Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however purification achieved using column chromatography on the Biotage® Horizon system on a 25S column eluting in a gradient of 5-20% EtOAc/*i*-hex.

LC/MS t=4.28 min [MH^+] 598/600.

b) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid.

^{1}H-NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.71 (2H, s), 6.10 (1H, d, J=3Hz), 6.22 (1H, d, J=3Hz), 6.62 (2H, t, J=9Hz), 6.73 (1H, d, J=9Hz), 7.28 (1H, dd, J=2Hz, 9Hz), 7.34 (1H,d, J=3Hz), 7.42 (1H, s), 7.90 (1H, s), 8.21 (1H,s).

LC/MS t=3.98 min [MH^+] 584/586.

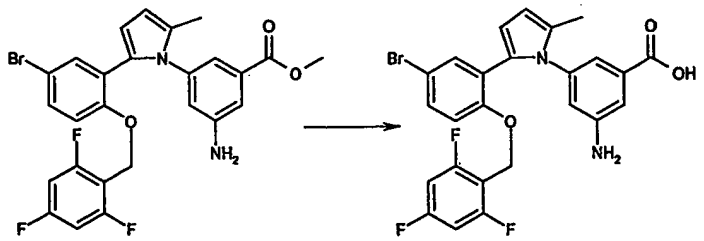
<u>Example 197 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid</u>

a) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester

Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however purification achieved using column chromatography on the Biotage® Horizon system on a 25S column eluting in a gradient of 20-60% EtOAc/*i*-hex.

LC/MS t=3.89 min [MH^+] 545/547.

b) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid.

^{1}H-NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 4.81 (2H, s), 4.90-6.00 (2H, broad s), 6.03 (1H, d, J=3Hz), 6.25 (1H, d, J=3Hz), 6.47 (1H, t, J=1Hz), 6.65 (2H, t, J=8Hz), 6.77 (1H, d, J=9Hz), 7.19-7.25 (3H, m), 7.28-7.31 (1H, m),

LC/MS t=3.54 min [MH^+] 531/533.

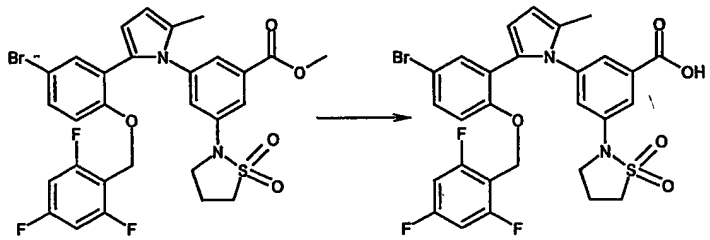
Example 198 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid

a) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester

Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however purification achieved using column chromatography on the Biotage® Horizon system on a 25S column eluting in a gradient of 20-60% EtOAc/*i*-hex.

LC/MS t=3.89 min [MH^+] 649/651.

b) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid, however further purification was required using column chromatography on the Biotage® Horizon system on a 25S reverse phase column eluting in a gradient of 30-100% MeCN/H_2O.

^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 2.45-2.55 (2H, m), 3.36 (2H, t, J=8Hz), 3.60 (2H, t, J=7Hz), 4.76 (2H, s), 6.05 (1H, d, J=3Hz), 6.21 (1H, d, J=3Hz), 6.63 (2H, t, J=8Hz), 6.75 (1H, d, J=9Hz), 7.11-7.14 (1H,m), 7.25-7.30 (1H+$CDCl_3$, m), 7.32 (1H, d, J=3Hz), 7.50-7.52 (1H, m), 7.77 (1H, m).

LC/MS t=3.56 min [MH^+] 635/637.

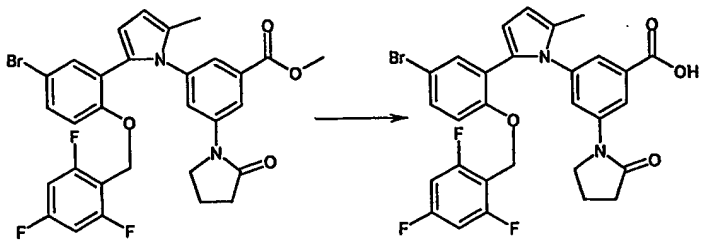
Example 199 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid

a) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester

Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however purification achieved using column chromatography on the Biotage® Horizon system on a 25S column eluting in a gradient of 20-60% EtOAc/*i*-hex.

LC/MS t=3.92 min [MH^+] 613/615.

b) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid.

^{1}H-NMR (400MHz, *d*6-DMSO) 2.06 (3H, s), 2.47-2.55 (4H, m), 3.68-3.76 (2H, m), 4.79 (2H, s), 6.00-6.04 (1H, m), 6.15 (1H, d, J=3Hz), 7.01 (1H, d, J=9Hz), 7.13-7.25 (4H, m), 7.37 (1H, d, J=9Hz), 7.57 (1H, s), 8.12 (1H, s).

LC/MS t=3.60 min [MH$^+$] 599/601.

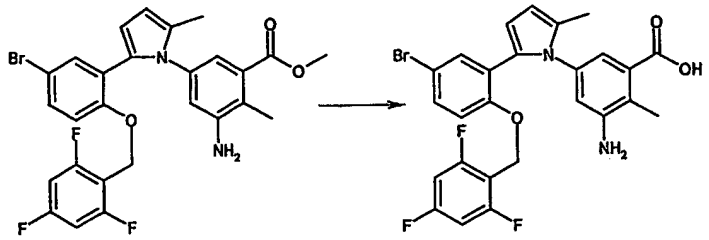
Example 200 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid

a) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid methyl ester

Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine, however purification achieved using column chromatography on the Biotage® Horizon system on a 25S column eluting in a gradient of 20-60% EtOAc/*i*-hex.

LC/MS t=3.93 min [MH$^+$] 559/561.

b) 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid

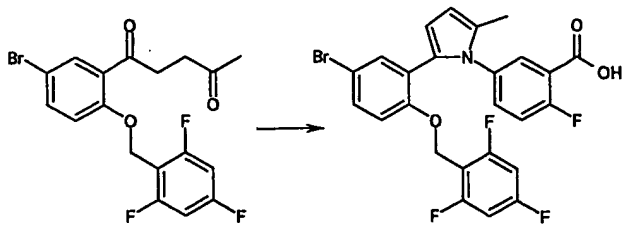


Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid, however further purification was required using column chromatography on the Biotage® Horizon system on a 25S reverse phase column eluting in a gradient of 30-100% MeCN/H_2O.

^{1}H-NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 2.39 (3H, s), 4.82 (2H, s), 6.02 (1H, d, J=3Hz), 6.22 (1H, d, J=3Hz), 6.45 (1H, s), 6.61-6.71 (2H, m), 6.77 (1H, d, J=9Hz), 7.17 (1H, s), 7.19-7.32 (2H+$CDCl_3$, m).

LC/MS t=3.55 min [MH$^+$] 545/547.

Example 201 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid

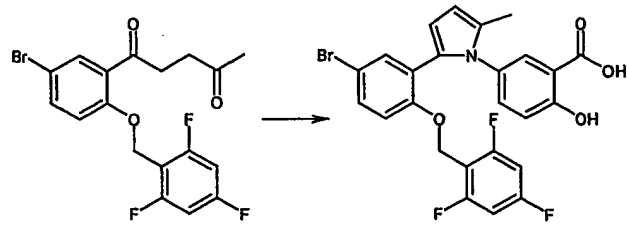


Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, however purification achieved using column chromatography on the Biotage® QUAD 4 system on a 25S column eluting in 25% EtOAc/*i*-hex (+AcOH).

^{1}H-NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 4.77 (2H, s), 6.07 (1H, d, J=3Hz), 6.20 (1H, d, J=3Hz), 6.65 (2H, t, J=9Hz), 6.74 (1H, d, J=9Hz), 6.99-7.06 (1H, m), 7.08-7.14 (1H, m), 7.25-7.32 (2H+$CDCl_3$, m), 7.68-7.72 (1H, m).

LC/MS t=3.78 min [MH^+] 534/536.

Example 202 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid

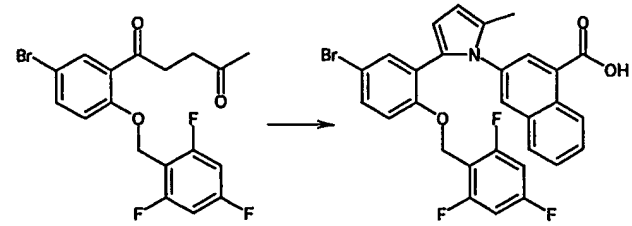


Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid, however purification achieved using column chromatography on the Biotage® QUAD 4 system on a 25S column eluting in 40% EtOAc/*i*-hex (+AcOH).

^{1}H-NMR (400MHz, MeOD) 2.05 (3H, s), 4.81 (2H, s), 5.96 (1H, d, J=3Hz), 6.08 (1H, d, J=3Hz), 6.78 (1H, d, J=9Hz), 6.81-6.91 (4H, m), 6.99 (1H, dd, J=2Hz, 9Hz), 7.23 (1H, s), 7.29 (1H, dd, J=2Hz, 9Hz), 7.42 (1H, d, 2Hz).

LC/MS t=4.18 min [MH^+] 532/534.

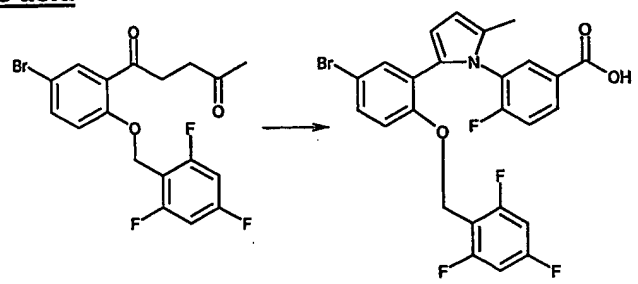
Example 203 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-naphthalene-1-carboxylic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, however purification achieved using column chromatography on the Biotage® QUAD 4 system on a 25S column eluting in 25% EtOAc/*i*-hex (+AcOH).

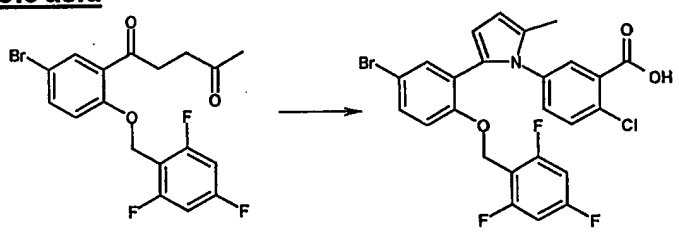
LC/MS t=3.95 min [MH^+] 566/568.

Example 204 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-4-fluoro-benzoic acid



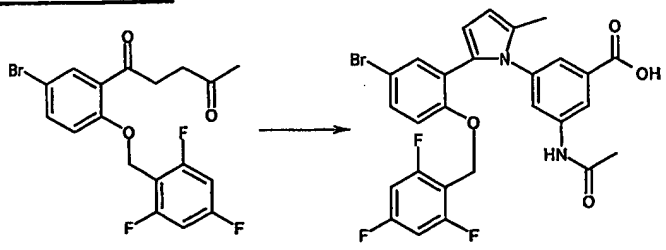
Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, however purification achieved using column chromatography on the Biotage® QUAD 4 system on a 25S column eluting in 25% EtOAc/*i*-hex (+AcOH).
LC/MS t=3.75 min [MH^+] 534/536.

Example 205 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, however purification achieved using column chromatography on the Biotage® QUAD 4 system on a 25S column eluting in 25% EtOAc/*i*-hex (+AcOH).
LC/MS t=3.89 min [MH^+] 550/552.

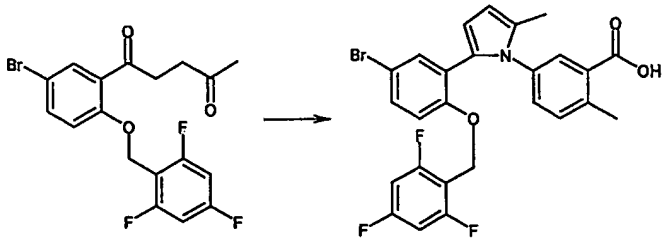
Example 206 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-acetylamino-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, however purification achieved using column chromatography on the Biotage® QUAD 4 system on a 25S column eluting in 40% EtOAc/*i*-hex (+AcOH).

^{1}H-NMR (400MHz, MeOD) 2.11 (6H, s), 4.76 (2H, s), 6.0 (1H, d, J=3Hz), 6.12 (1H, d, J=3Hz), 6.79-6.88 (3H, m), 7.24-7.31 (3H, m), 7.49 (1H, s), 8.07 (1H, s).
LC/MS t=3.53 min [MH$^+$] 573/575.

Example 207 3-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, however purification achieved using column chromatography on the Biotage® QUAD 4 system on a 25S column eluting in 25% EtOAc/*i*-hex (+AcOH).
^{1}H-NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 2.64 (3H, s), 4.76 (2H, s), 6.07 (1H, d, J=3Hz), 6.23 (1H, d, J=3Hz), 6.61-6.70 (2H, m), 6.74 (1H, d, J=9Hz), 7.00 (1H, dd, J=2Hz, 8Hz), 7.13 (1H, d, J=9Hz), 7.23-7.29 (2H+$CDCl_3$, m), 7.76 (1H, d, J=2Hz).
LC/MS t=3.81 min [MH$^+$] 530/532.

Example 208 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid

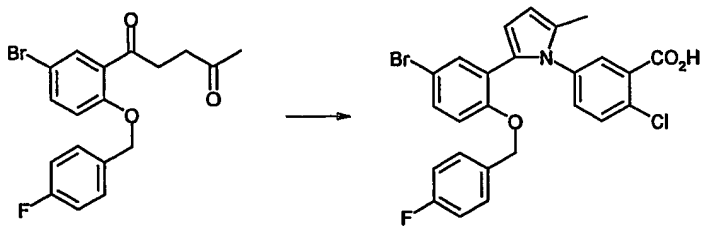
a) 5-Bromo-2-(4-fluoro-benzyloxy)-benzaldehyde

Procedure as for 2-benzyloxy-5-chloro-benzaldehyde using the appropriate benzyl bromide to give the title compound.
LCMS t=3.60 min.

b) 1-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione

Procedure as for 1-[5-chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione to give the title compound.
LC/MS t=3.57min

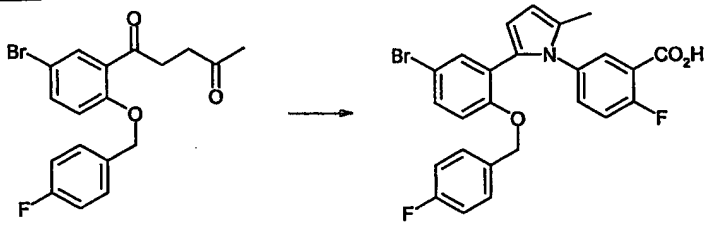
c) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid



1-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.15g, 0.40mmol), 5-amino-2-chloro-benzoic acid (0.068g, 0.40mmol) and *p*-TSA (cat.) in NMP (2ml) were heated in a sealed vessel at 180°C for 15 minutes using microwaves. Upon cooling the reaction was diluted with CH_2Cl_2 (25ml) and shaken with dil. HCl (1ml). The organics were separated

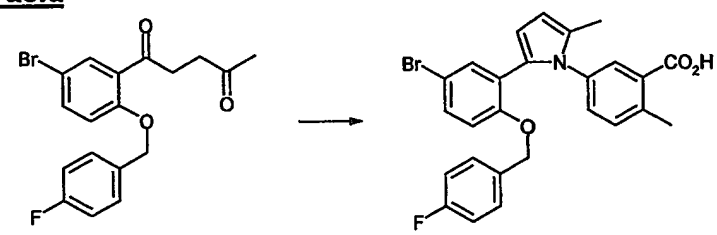
using a phase separator column with a $NaSO_4$ cartridge attached and concentrated. The residue was purified by column chromatography using a Si SPE cartridge (5g) eluting in 0-50% EtOAc/*i*-hex. to give the title compound (133mg, 65%).
^{1}H-NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 4.68 (2H, s), 6.13 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.54 (1H, d, J=9Hz), 6.94-7.05 (5H, m), 7.22-7.31 (2H, m), 7.45 (1H, d, J=2.5Hz), 7.63 (1H, d, J=2.5Hz).
LC/MS t=4.24 min [MH^+] 514/516/518.

Example 209 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid



1-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.10g, 0.26mmol), 5-amino-2-fluoro-benzoic acid (0.041g, 0.26mmol) and *p*-TSA (cat.) in NMP (1ml) were heated in a sealed vessel at 180°C for 10 minutes using microwaves. Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by MDAP to give the title compound (60mg, 46%).
^{1}H-NMR (400MHz, *d*6-DMSO) 2.06 (3H, s), 4.84 (2H, s), 6.06 (1H, dd, J=1, 3Hz), 6.22 (1H, d, J=3Hz), 6.83 (1H, d, J=9Hz), 7.12-7.22 (4H, m), 7.24-7.35 (4H, m), 7.41-7.45 (1H, m), 13.40 (1H, s).
LC/MS t=4.06 min [MH^+] 498/500.

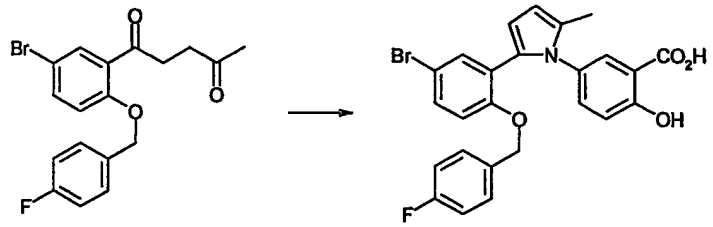
Example 210 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid



1-[5-Bromo-2-(4-Fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.10g, 0.26mmol), 5-amino-2-methyl-benzoic acid (0.04g, 0.26mmol) and *p*-TSA (cat.) in NMP (1ml) were heated in a sealed vessel at 180°C for 10 minutes using microwaves. Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by MDAP to give the title compound (44mg, 34%).
^{1}H-NMR (400MHz, *d*6-DMSO) 2.05 (3H, s), 2.50 (excess, s), 4.84 (2H, s), 6.04 (1H, dd, J=1, 3Hz), 6.20 (1H, d, J=3Hz), 6.81 (1H, d, J=9Hz), 7.08-7.19 (5H, m), 7.21-7.32 (3H, m), 7.45 (1H, d, J=2Hz), 12.95 (1H, s).

LC/MS t=4.05 min [MH^+] 494/496.

Example 211 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid

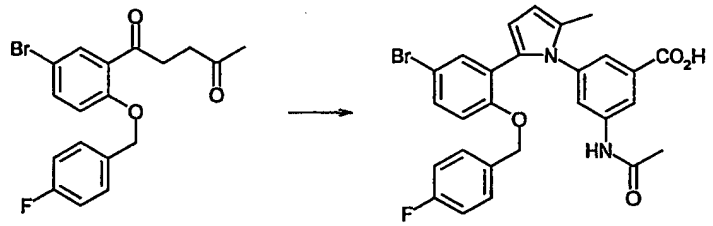


1-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.30g, 0.78mmol), 5-amino-2-hydroxy-benzoic acid (0.120g, 0.78mmol) and *p*-TSA (cat.) in NMP (3ml) were heated in a sealed vessel at 180°C for 10 minutes using microwaves. Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by MDAP to give the title compound (78mg, 20%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 4.74 (2H, s), 6.11 (1H, dd, J=1, 3Hz), 6.27 (1H, d, J=3Hz), 6.54 (1H, d, J=9Hz), 6.82 (1H, d, J=9Hz), 6.96-7.02 (2H, m), 7.03-7.08 (3H, m), 7.21 (1H, dd, J=3, 9Hz), 7.39 (1H, d, J=3Hz), 7.53 (1H, d, J=3Hz), 10.60 (1H, s).

LC/MS t=4.87 min [MH$^+$] 494/496.

Example 212 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-acetylamino-benzoic acid

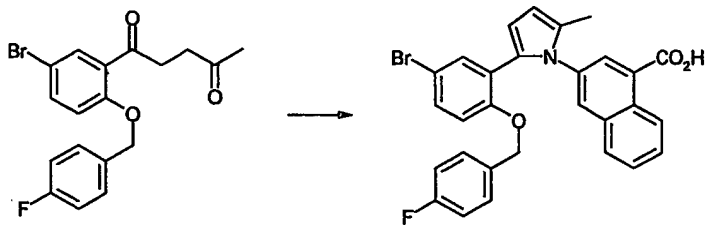


1-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.30g, 0.78mmol), 3-acetylamino-5-amino-benzoic acid (0.153g, 0.78mmol) and *p*-TSA (cat.) in NMP (3ml) were heated in a sealed vessel at 180°C for 10 minutes using microwaves. Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by MDAP to give the title compound (89mg, 21%).

^{1}H-NMR (400MHz, *d*6-DMSO) 2.03 (3H, s), 2.07 (3H, s), 4.83 (2H, s), 6.06 (1H, dd, J=1, 3Hz), 6.23 (1H, d, J=3Hz), 6.82 (1H, d, J=9Hz), 7.09-7.21 (6H, m), 7.30 (1H, dd, J=3, 9Hz), 7.59 (1H, d, J=3Hz), 8.09 (1H, m), 10.10 (1H, s), 13.10 (1H, s).

LC/MS t=3.69 min [MH$^+$] 537/539.

Example 213 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-1-napthoic acid

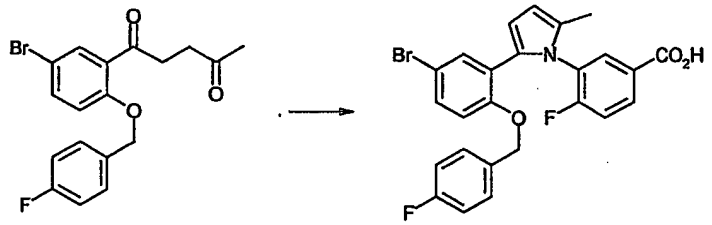


1-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.10g, 0.26mmol), 3-amino-napthalene-1-carboxylic acid (0.049g, 0.78mmol) and *p*-TSA (cat.) in NMP (1ml) were heated in a sealed vessel at 180°C for 10 minutes using microwaves. Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by MDAP to give the title compound (79mg, 56%).

^{1}H-NMR (400MHz, *d*6-DMSO) 2.12 (3H, s), 4.76 (2H, s), 6.12 (1H, dd, J=1, 3Hz), 6.27 (1H, d, J=3Hz), 6.73 (1H, d, J=9Hz), 6.99-7.08 (4H, m), 7.27 (1H, dd, J=3, 9Hz), 7.34 (1H, d, J=3Hz), 7.56-7.69 (2H, m), 7.76 (1H, d, J=3Hz), 7.86-7.91 (2H, m), 8.86 (1H, d, J=9Hz), 13.25 (1H, s).

LC/MS t=4.21 min [MH^+] 530/532.

Example 214 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-4-fluoro-benzoic acid



1-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.10g, 0.26mmol), 3-amino-4-fluoro-benzoic acid (0.041g, 0.26mmol) and *p*-TSA (cat.) in NMP (1ml) were heated in a sealed vessel at 180°C for 10 minutes using microwaves. Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by MDAP to give the title compound (36mg, 27%).

^{1}H-NMR (400MHz, *d*6-DMSO) 2.01 (3H, s), 4.85 (2H, dd, J=12Hz), 6.09 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.83 (1H, d, J=9Hz), 7.11-7.24 (5H, m), 7.31 (1H, dd, J=3, 9Hz), 7.40 (1H, t, J=9Hz), 7.60 (1H, dd, J=2, 8Hz), 7.92-7.97 (1H, m), 13.25 (1H, s).

LC/MS t=4.01 min [MH^-] 496/498.

Example 215 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid

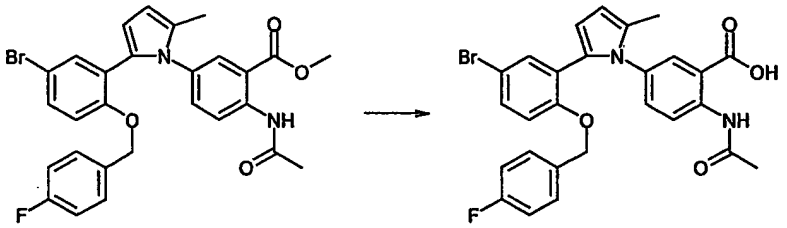
a) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester

1-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.10g, 0.26mmol), 2-acetylamino-5-amino-benzoic acid methyl ester (0.055g, 0.26mmol) and *p*-TSA (cat.) in NMP (1ml) were heated in a sealed vessel at 180°C for 10 minutes using microwaves.

Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography using a Si SPE cartridge (5g) eluting in 1-20% EtOAc/*i*-hex. to give the title compound (96mg, 66%).

LC/MS t=3.85 min [MH^+] 551/553.

b) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid



3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester (0.095g, 0.17mmol) was dissolved in methanol (6ml) and 2M NaOH (0.6ml) and was heated in a sealed vessel at 100°C for 60 seconds in a microwave. Upon cooling the reaction was concentrated *in vacuo*, diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a Na_2SO_4 cartridge attached and concentrated to give the title compound (93mg, 100%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.01 (3H, s), 2.20 (3H, s), 4.68 (2H, s), 6.11 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.53 (1H, d, J=9Hz), 6.93-7.00 (2H, m), 7.01-7.07 (2H, m), 7.12 (1H, dd, J=3, 9Hz), 7.19 (1H, dd, J=3, 9Hz), 7.40 (1H, d, J=3Hz), 7.69 (1H, d, J=3Hz), 8.55 (1H, m), 10.95 (1H, s).

LC/MS t=4.30 min [MH^+] 537/539.

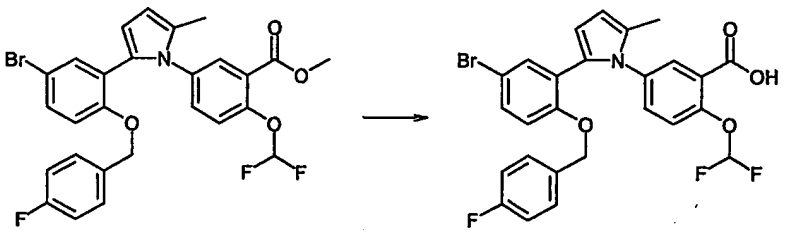
<u>Example 216 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid</u>

a) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid methyl ester

1-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.10g, 0.26mmol), 5-amino-2-difluoromethoxy-benzoic acid methyl ester (0.057g, 0.26mmol) and *p*-TSA (cat.) in NMP (1ml) were heated in a sealed vessel at 180°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography using a Si SPE cartridge (5g) eluting in 1-20% EtOAc/*i*-hex. to give the title compound (45mg, 30%).

LC/MS t=4.21 min [MH^+] 560/562.

b) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid



3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid methyl ester (0.045g, 0.08mmol) was dissolved in methanol (6ml) and 2M NaOH (0.6ml) and was heated in a sealed vessel at 100°C for 60 seconds using a microwave. Upon cooling the reaction was concentrated *in vacuo*, diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated to give the title compound (42mg, 96%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 4.65 (2H, s), 6.12 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.53 (1H, d, J=9Hz), 6.55 (1H, t, J=74Hz), 6.93-6.99 (2H, m), 7.01-7.08 (4H, m), 7.21 (1H, dd, J=3, 9Hz), 7.39 (1H, d, J=3Hz), 7.61 (1H, d, J=2Hz).

LC/MS t=4.13 min [MH^+] 546/548.

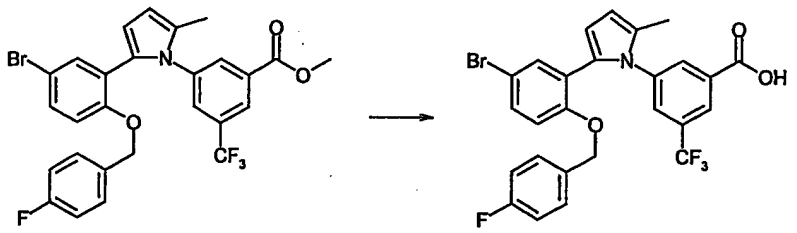
Example 217 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid

a) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester

1-[5-Bromo-2-(4-Fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.10g, 0.26mmol), 3-amino-5-trifluoromethyl-benzoic acid methyl ester (0.055g, 0.26mmol) and *p*-TSA (cat.) in NMP (1ml) were heated in a sealed vessel at 180°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography using a Si SPE cartridge (5g) eluting in 1-20% EtOAc/*i*-hex. to give the title compound (50mg, 34%).

LC/MS t=4.39 min [MH^+] 562/564.

b) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid



3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester (0.050g, 0.09mmol) was dissolved in methanol (6ml) and 2M NaOH (0.6ml) and was heated in a sealed vessel at 100°C for 60 seconds using a microwave. Upon cooling the reaction was concentrated *in vacuo*, diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase

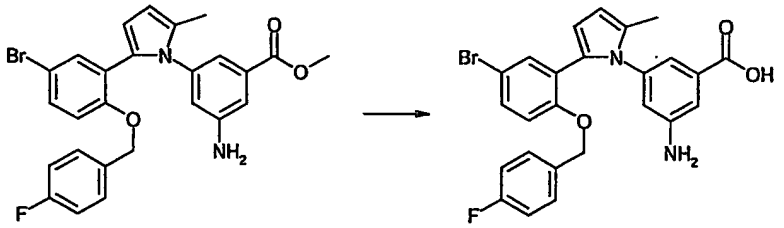
separator column with a $NaSO_4$ cartridge attached and concentrated to give the title compound (38mg, 80%).
^{1}H-NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.64 (2H, s), 6.17 (1H, dd, J=0.5, 3Hz), 6.31 (1H, d, J=3Hz), 6.53 (1H, d, J=9Hz), 6.93-7.04 (4H, m), 7.24 (1H, dd, J=3, 9Hz), 7.40 (1H, m), 7.45 (1H, d, J=2.5Hz), 7.85 (1H, s), 8.18 (1H, m).
LC/MS t=4.39 min [MH^+] 548/550.

Example 218 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid

a) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester

1-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (1.0g, 2.6mmol), 3,5-diamino-benzoic acid methyl ester (0.44g, 2.6mmol) and *p*-TSA (cat.) in NMP (5ml) were heated in a sealed vessel at 180°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography using a Si SPE cartridge (10g) eluting in 1-20% EtOAc/*i*-hex. to give the title compound (750mg, 56%).
LC/MS t=3.99 min [MH^+] 509/511.

b) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid



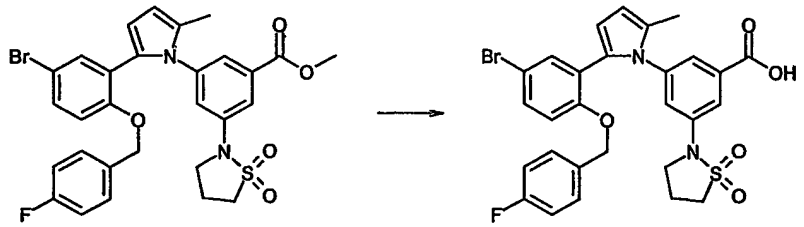
3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester (0.15g, 0.23mmol) was dissolved in methanol (6ml) and 2M NaOH (0.6ml) and was heated in a sealed vessel at 120°C for 5 minutes using a microwave. Upon cooling the reaction was concentrated *in vacuo*, diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated to give the title compound (110mg, 97%).
^{1}H-NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 4.74 (2H, s), 6.10 (1H, dd, J=0.5, 3Hz), 6.28 (1H, d, J=3Hz), 6.43 (1H, t, J=2Hz), 6.55 (1H, d, J=9Hz), 6.93-7.01 (2H, m), 7.05-7.11 (2H, m), 7.16 (1H, t, J=1.5Hz), 7.19 (1H, dd, J=3, 9Hz), 7.24-7.27 (1H, m), 7.36 (1H, d, J=2.5Hz).
LC/MS t=3.79 min [MH^+] 495/497.

Example 219 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*isothiazolidin*-2-yl)-benzoic acid

a) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*isothiazolidin*-2-yl)-benzoic acid methyl ester

1-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.10g, 0.26mmol), 3-amino-5-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-benzoic acid methyl ester (0.071g, 0.26mmol) and *p*-TSA (cat.) in NMP (1ml) were heated in a sealed vessel at 180°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography using a Si SPE cartridge (5g) eluting in 1-20% EtOAc/*i*-hex. to give the title compound (108mg, 67%).
LC/MS t=3.98 min [MH^+] 613/615.

b) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-benzoic acid



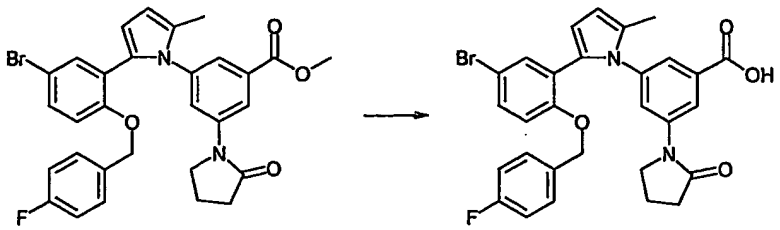
3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-benzoic acid methyl ester (0.108g) was dissolved in methanol (6ml) and 2M NaOH (0.6ml) and was heated in a sealed vessel at 100°C for 60 seconds using a microwave. Upon cooling the reaction was concentrated *in vacuo*, diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated to give the title compound (100mg, 95%).
^{1}H-NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 2.48 (2H, quin, J=9Hz), 3.34 (2H, t, J=8.5Hz), 3.50 (2H, t, J=8.5Hz), 4.71 (2H, s), 6.13 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.53 (1H, d, J=9Hz), 6.92-6.99 (2H, m), 7.00-7.05 (2H, m), 7.11 (1H, t, J=2Hz), 7.21 (1H, dd, J=3, 9Hz), 7.42 (1H, d, J=2.5Hz), 7.48 (1H, t, J=2Hz), 7.76 (1H, t, J=2Hz).
LC/MS t=3.84 min [MH^+] 599/601.

<u>Example 220 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid</u>

a) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester

1-[5-Bromo-2-(4-fluoro-benzyloxy)- phenyl]-pentane-1,4-dione (0.10g, 0.26mmol), 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (0.062g, 0.26mmol) and *p*-TSA (cat.) in NMP (1ml) were heated in a sealed vessel at 180°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography using a Si SPE cartridge (5g) eluting in 1-20% EtOAc/*i*-hex. to give the title compound (94mg, 67%).
LC/MS t=4.02 min [MH^+] 577/579.

b) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid



3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (0.094g, 0.16mmol) was dissolved in methanol (6ml) and 2M NaOH (0.6ml) and was heated in a sealed vessel at 100°C for 60 seconds using a microwave. Upon cooling the reaction was concentrated *in vacuo*, diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated to give the title compound (90mg, 100%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.10 (2H, quin, J=8Hz), 2.19 (3H, s), 2.57 (2H, t, J=8Hz), 3.58 (2H, t, J=7.5Hz), 4.71 (2H, s), 6.13 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.52 (1H, d, J=9Hz), 6.92-6.98 (2H, m), 7.00-7.06 (2H, m), 7.19 (1H, dd, J=3, 9Hz), 7.40 (1H, d, J=2.5Hz), 7.49 (1H, t, J=2Hz), 7.57 (1H, t, J=2Hz), 8.17 (1H, t, J=1.5Hz).

LC/MS t=3.89 min [MH^+] 563/565.

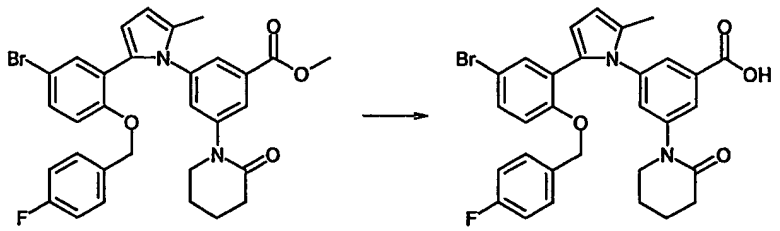
Example 221 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid

a) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester

1-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.10g, 0.26mmol), 3-amino-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (0.065g, 0.26mmol) and *p*-TSA (cat.) in NMP (1ml) were heated in a sealed vessel at 180°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography using a Si SPE cartridge (5g) eluting in 1-20% EtOAc/*i*-hex. to give the title compound (47mg, 30%).

LC/MS t=3.96 min [MH^+] 591/593.

b) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid



3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (0.047g, 0.08mmol) was dissolved in methanol (6ml) and 2M NaOH (0.6ml) and was heated in a sealed vessel at 100°C for 60 seconds using a microwave. Upon cooling the reaction was concentrated *in vacuo*, diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase

separator column with a $NaSO_4$ cartridge attached and concentrated to give the title compound (45mg, 100%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.60-1.67 (4H, m), 2.02 (3H, s), 2.27-2.32 (2H, m), 3.02-3.09 (2H, m), 4.60 (2H, s), 6.02 (1H, d, J=3Hz), 6.25 (1H, d, J=3Hz), 6.43 (1H, d, J=9Hz), 6.71 (1H, s), 6.86-6.97 (2H, m), 6.99-7.05 (3H, m), 7.24 (1H, d, J=3Hz), 7.58 (1H, s), 7.84 (1H, s).

LC/MS t=3.96 min [MH^+] 591/593.

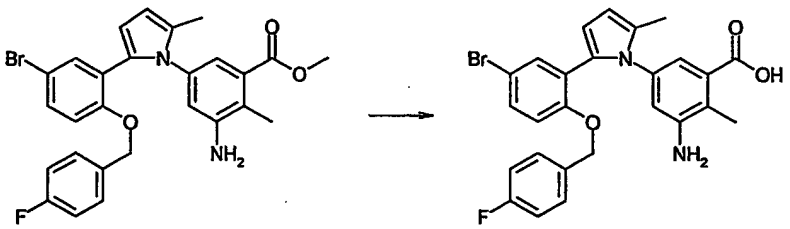
Example 222 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid

a) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid methyl ester

1-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.10g, 0.26mmol), 3,5-diamino-2-methyl-benzoic acid methyl ester (0.047g, 0.26mmol) and *p*-TSA (cat.) in NMP (1ml) were heated in a sealed vessel at 180°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with EtOAc (25ml) and washed with dil. $NaHCO_3$, dil. HCl and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography using a Si SPE cartridge (5g) eluting in 1-20% EtOAc/*i*-hex. to give the title compound (70mg, 52%).

LC/MS t=4.02 min [MH^+] 523/525.

b) 3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid



3-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-2-methyl-benzoic acid methyl ester (0.070g, 0.13mmol) was dissolved in methanol (6ml) and 2M NaOH (0.6ml) and was heated in a sealed vessel at 120°C for 5 minutes using a microwave. Upon cooling the reaction was concentrated *in vacuo*, diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated to give the title compound (66mg, 97%).

^{1}H-NMR (400MHz, $CDCl_3$) 1.83 (3H, s), 1.87 (3H, s), 3.21 (2H, broad s), 4.69 (2H, s), 5.93 (1H, d, J=3Hz), 6.12 (1H, d, J=2Hz), 6.24 (1H, d, J=3Hz), 6.39 (1H, d, J=9Hz), 6.63 (1H, d, J=2Hz), 6.83-6.91 (3H, m), 7.02-7.08 (2H, m), 7.13 (1H, d, J=2.5Hz).

LC/MS t=3.81 min [MH^+] 509/511.

Example 223 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid

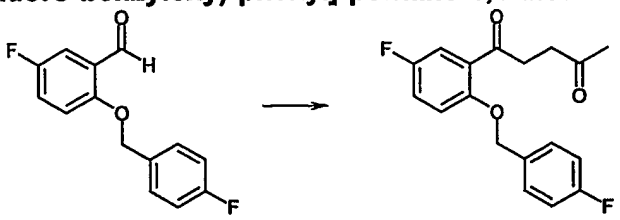
a) 5-Fluoro-2-(4-fluoro-benzyloxy)-benzaldehyde

5-Fluorosalicylaldehyde (4.8g, 34.3mmol), 4-fluorobenzyl bromide (4.32ml, 34.3mmol) and K_2CO_3 (9.5g, 68.6mmol) were heated in DMF (50ml) at 50°C for 30mins. Upon cooling to room temperature, EtOAc and sat. NH_4Cl were added. The layers were separated and the aqueous phase was extracted with EtOAc (x2). The combined organic extracts were washed with water, dried ($MgSO_4$), filtered and concentrated to give the title compound (8.4g, 98%).

^{1}H NMR (400MHz, $CDCl_3$) 5.14 (2H, s), 7.01 (1H, dd, J=4, 9Hz), 7.07-7.14 (2H, m), 7.22-7.28 (1H, m), 7.37-7.44 (2H, m), 7.53 (1H, dd, J=3.5, 8Hz), 10.45 (1H, s).

LC/MS t=3.45 min.

b) 1-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione

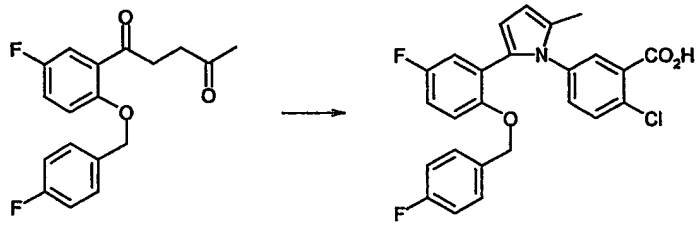


A mixture of 5-Fluoro-2-(4-fluoro-benzyloxy)-benzaldehyde (6.4g, 25.8mmol), methyl vinyl ketone (2.19ml, 26.3mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (1.95g, 7.7mmol) and triethylamine (10.7ml, 77mmol) was heated in ethanol (5ml) at 80°C for 16 hours. Upon cooling, the mixture was diluted with EtOAc (100ml) and washed with saturated NH_4Cl, brine, dried (Na_2SO_4) filtered and concentrated. The residue was purified by chromatography using Biotage with *iso*-hexane containing a gradient of EtOAc (5-20%) to give the title compound as an oil (5.68g, 69%).

^{1}H NMR (400MHz, $CDCl_3$) 2.19 (3H, s), 2.78 (2H, t, J=6Hz), 3.22 (2H, t, J=6Hz), 5.10 (2H, s), 6.96 (1H, dd, J=4, 9Hz), 7.05-7.17 (3H, m), 7.38-7.48 (3H, m).

LC/MS t=3.17min

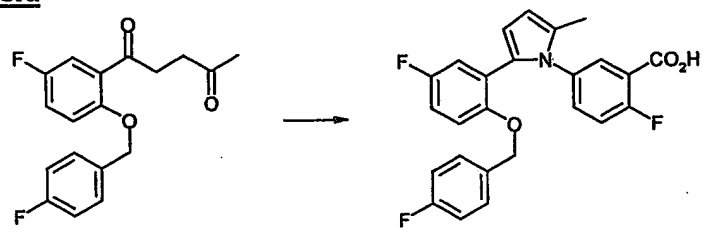
c) 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid



1-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.15g, 0.47mmol), 5-amino-2-chloro-benzoic acid (0.081g, 0.47mmol) and *p*-TSA (cat.) in CH_3CN (1ml) were heated in a sealed vessel at 160°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a Na_2SO_4 cartridge attached and concentrated. The residue was purified by column chromatography using Biotage reverse phase 25M cartridge, with water / CH_3CN (30-100%) as eluant, to give the title compound (94mg, 44%).

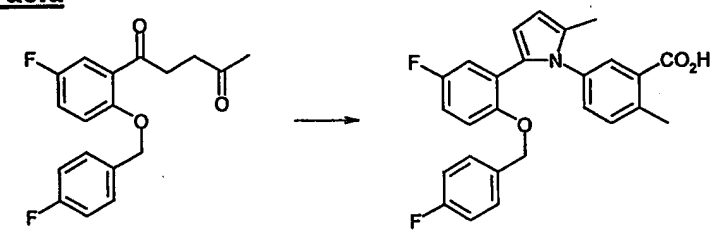
^{1}H-NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 4.67 (2H, s), 6.14 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.62 (1H, dd, J=3, 9Hz), 6.84 (1H, m), 6.94-7.07 (6H, m), 7.25-7.30 (1H excess, m), 7.60 (1H, d, J=2.5Hz).
LC/MS t=3.79 [MH^+] 454/456.

Example 224 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid



1-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.15g, 0.47mmol), 5-amino-2-fluoro-benzoic acid (0.073g, 0.47mmol) and *p*-TSA (cat.) in CH_3CN (1ml) were heated in a sealed vessel at 160°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a Na_2SO_4 cartridge attached and concentrated. The residue was purified by column chromatography using Biotage reverse phase 25M cartridge, with water / CH_3CN (30-100%) as eluant, to give the title compound (142mg, 69%).
^{1}H-NMR (400MHz, *d*6-DMSO) 2.14 (3H, s), 4.70 (2H, s), 6.13 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.63 (1H, dd, J=4, 9Hz), 6.80-6.87 (1H, m), 6.94-7.03 (4H, m), 7.05-7.12 (3H, m), 7.63 (1H, dd, J=2.5, 7Hz).
LC/MS t=3.88 min [MH^+] 438.

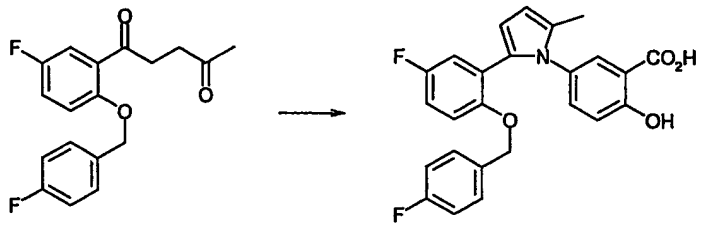
Example 225 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid



1-[5-Fluoro-2-(4-fluoro-benzyloxy)- phenyl]-pentane-1,4-dione (0.15g, 0.47mmol), 5-amino-2-methyl-benzoic acid (0.071g, 0.47mmol) and *p*-TSA (cat.) in CH_3CN (1ml) were heated in a sealed vessel at 160°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated. The residue was purified by column chromatography using Biotage reverse phase 25M cartridge, with water / CH_3CN (30-100%) as eluant, to give the title compound (142mg, 69%).

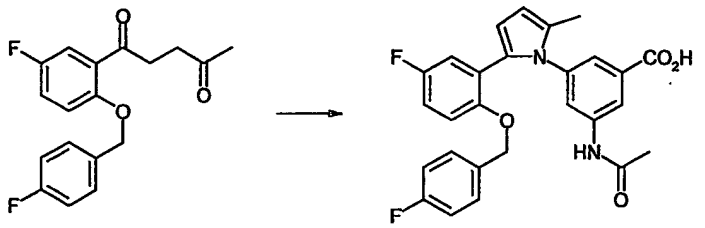
^{1}H-NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 2.61 (3H, s), 4.71 (2H, s), 6.12 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.60 (1H, dd, J=4, 9Hz), 6.76-6.82 (1H, m), 6.91-7.02 (4H, m), 7.04-7.12 (3H, m), 7.71 (1H, d, J=2Hz).
LC/MS t=3.89 min [MH^+] 434.

Example 226 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid



1-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.30g, 0.94mmol), 5-amino-2-hydroxy-benzoic acid (0.144g, 0.94mmol) and *p*-TSA (cat.) in CH_3CN (2ml) were heated in a sealed vessel at 160°C for 10 minutes using microwaves. Upon cooling the reaction was diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated. The residue was purified by column chromatography using Biotage reverse phase 25M cartridge, with water / CH_3CN (30-100%) as eluant, to give the title compound (256mg, 62%).
^{1}H-NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 4.73 (2H, s), 6.12 (1H, d, J=3.5Hz), 6.30 (1H, d, J=3.5Hz), 6.63 (1H, dd, J=4.5, 9Hz), 6.78-6.85 (2H, m), 6.92-7.03 (3H, m), 7.05-7.12 (3H, m), 7.52 (1H, d, J=2.5Hz), 10.40 (1H, s).
LC/MS t=4.47 min [MH^+] 436.

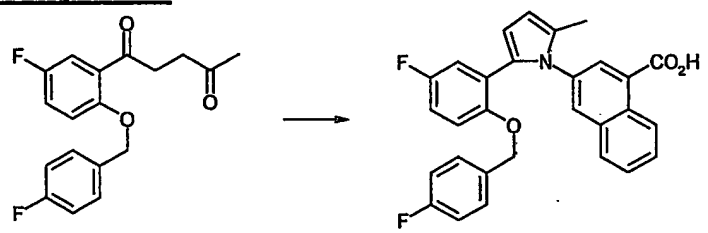
Example 227 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-acetylamino-benzoic acid



1-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.30g, 0.94mmol), 3-acetylamino-5-amino-benzoic acid (0.183g, 0.94mmol) and *p*-TSA (cat.) in CH_3CN (2ml) were heated in a sealed vessel at 160°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated. The residue was purified by column chromatography using Biotage reverse phase 25M cartridge, with water / CH_3CN (30-100%) as eluant, to give the title compound (347mg, 77%).

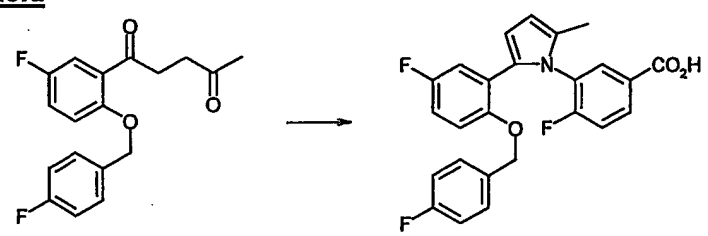
^{1}H-NMR (400MHz, $CDCl_3$) 2.01 (3H, s), 2.08 (3H, s), 4.70 (2H, s), 6.12 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.61 (1H, dd, J=4.5, 9Hz), 6.76-6.82 (1H, m), 6.91-7.02 (3H, m), 7.06-7.14 (3H, m), 7.42 (1H, s), 7.51 (1H, s), 7.96 (1H, s).
LC/MS t=3.56 min [MH^+] 477.

Example 228 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-napthalene-1-carboxylic acid



1-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.15g, 0.47mmol), 3-amino-napthalene-1-carboxylic acid (0.088g, 0.47mmol) and *p*-TSA (cat.) in CH_3CN (1ml) were heated in a sealed vessel at 160°C for 10 minutes using microwaves. Upon cooling the reaction was diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated. The residue was purified by column chromatography using Biotage reverse phase 25M cartridge, with water / CH_3CN (30-100%) as eluant, to give the title compound (52mg, 24%).
^{1}H-NMR (400MHz, $CDCl_3$) 2.21 (3H, s), 4.60 (2H, s), 6.19 (1H, d, J=3Hz), 6.36 (1H, d, J=3Hz), 6.50 (1H, dd, J=4.5, 9Hz), 6.73-6.80 (1H, m), 6.86-6.97 (4H, m), 7.09 (1H, dd, J=3, 9Hz), 7.48-7.68 (4H, m), 8.05 (1H, d, J=2Hz), 9.03 (1H, d, J=8.5Hz).
LC/MS t=4.04 min [MH^+] 470.

Example 229 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-4-fluoro-benzoic acid



1-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.15g, 0.47mmol), 3-amino-4-fluoro-benzoic acid (0.073g, 0.47mmol) and *p*-TSA (cat.) in CH_3CN (1ml) were heated in a sealed vessel at 160°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated. The residue was purified by column chromatography using Biotage reverse phase 25M cartridge, with water / CH_3CN (30-100%) as eluant, to give the title compound (94mg, 46%).

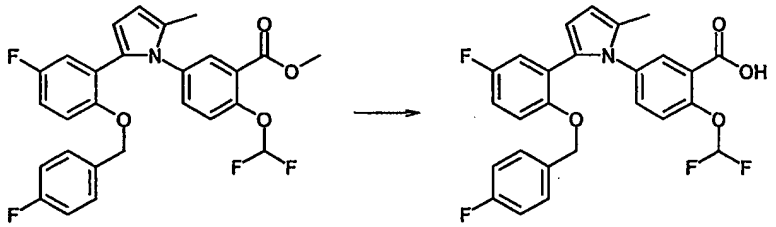
^{1}H-NMR (400MHz, $CDCl_3$) 2.11 (3H, s), 4.76 (2H, s), 6.16 (1H, d, J=3Hz), 6.34 (1H, d, J=3Hz), 6.58 (1H, dd, J=4, 9Hz), 6.74-6.80 (1H, m), 6.90-7.01 (3H, m), 7.05-7.13 (3H, m), 7.77 (1H, dd, J=2, 7Hz), 7.98-8.04 (1H,m).
LC/MS t=3.85 min [MH^+] 438.

Example 230 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid

a) 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid methyl ester

1-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.15g, 0.47mmol), 5-amino-2-difluoromethoxy-benzoic acid methyl ester (0.102g, 0.47mmol) and *p*-TSA (cat.) in CH_3CN (1ml) were heated in a sealed vessel at 160°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a Na_2SO_4 cartridge attached and concentrated. The residue was purified by column chromatography using Biotage 25M cartridge, with *iso*-hexane / EtOAc (5-50%) as eluant, to give the title compound (130mg, 55%).
LC/MS t=3.98 min [MH^+] 500.

b) 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid



3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid methyl ester (0.130g, 0.26mmol) was dissolved in ethanol (2ml) and 2M NaOH (0.5ml) and was heated in a sealed vessel at 120°C for 5 minutes using microwaves. Upon cooling the reaction was diluted with CH_2Cl_2 (8ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a Na_2SO_4 cartridge attached and concentrated to give the title compound (100mg, 79%).
^{1}HNMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.65 (2H, s), 6.14 (1H, d, J=3.5Hz), 6.30 (1H, d, J=3.5Hz), 6.59 (1H, t, J=74Hz), 6.62 (1H, dd, J=4.5, 9Hz), 6.80-6.87 (1H, m), 6.95-7.03 (3H, m), 7.04-7.11 (4H, m), 7.62-7.64 (1H, m).
LC/MS t =3.67 min [MH^+] 486.

Example 231 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid

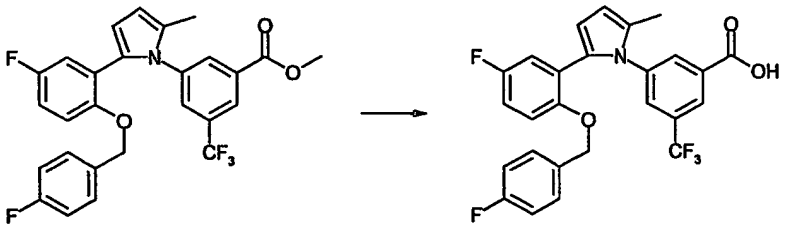
a) 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester

1-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.15g, 0.47mmol), 3-amino-5-trifluoromethyl-benzoic acid methyl ester (0.099g, 0.47mmol) and *p*-TSA (cat.) in CH_3CN

(1ml) were heated in a sealed vessel at 160°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated. The residue was purified by column chromatography using Biotage 25M cartridge, with *iso*-hexane / EtOAc (5-50%) as eluant, to give the title compound (110mg, 47%).

LC/MS t=4.16 min [MH^+] 502.

b) 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid



3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester (0.110g, 0.22mmol) was dissolved in ethanol (2ml) and 2M NaOH (0.5ml) and was heated in a sealed vessel at 120°C for 5 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (8ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a Na_2SO_4 cartridge attached and concentrated to give the title compound (97mg, 90%).

^{1}H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.61 (2H, s), 6.18 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.60 (1H, dd, J=4.5, 9Hz), 6.82-6.88 (1H, m), 6.94-7.06 (5H, m), 7.37 (1H, s), 7.83 (1H, s), 8.17 (1H, s).

LC/MS t=3.86 min [MH^+] 488.

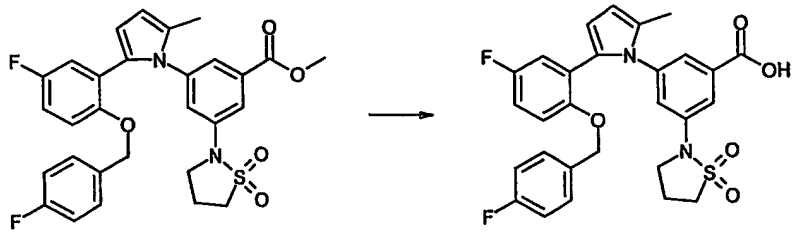
Example 232 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*isothiazolidin*-2-yl)-benzoic acid

a) 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*isothiazolidin*-2-yl)-benzoic acid methyl ester

1-[5-Fluoro-2-(4-fluoro-benzyloxy)- phenyl]-pentane-1,4-dione (0.15g, 0.47mmol), 3-amino-5-(1,1-dioxo-1λ^6-*isothiazolidin*-2-yl)-benzoic acid methyl ester (0.127g, 0.47mmol) and *p*-TSA (cat.) in CH_3CN (1ml) were heated in a sealed vessel at 160°C for 10 minutes using microwaves. Upon cooling the reaction was diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a Na_2SO_4 cartridge attached and concentrated. The residue was purified by column chromatography using Biotage 25M cartridge, with *iso*-hexane / EtOAc (15-80%) as eluant, to give the title compound (160mg, 61%).

LC/MS t=3.79 min [MH^+] 553.

b) 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*isothiazolidin*-2-yl)-benzoic acid



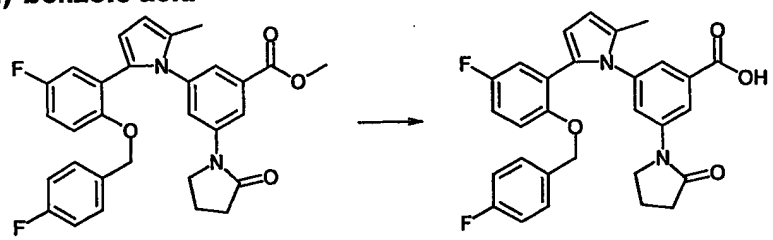
3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-benzoic acid methyl ester (0.160g, 0.29mmol) was dissolved in ethanol (2ml) and 2M NaOH (0.5ml) and was heated in a sealed vessel at 120°C for 5 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (8ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a Na_2SO_4 cartridge attached and concentrated to give the title compound (155mg, 100%).
^{1}H-NMR (400MHz, $CDCl_3$) 2.21 (3H, s), 2.49 (2H, quin, J=7Hz), 3.34 (2H, t, J=7Hz), 3.52 (2H, t, J=7Hz), 4.70 (2H, s), 6.14 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.61 (1H, dd, J=4.5, 9Hz), 6.78-6.95 (1H, m), 6.94-7.01 (3H, m), 7.03-7.09 (2H, m), 7.13-7.17 (1H, m), 7.45-7.47 (1H, m), 7.72-7.75 (1H, m).
LC/MS t=3.43 min [MH^+] 539.

Example 233 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid

a) 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester

1-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.15g, 0.47mmol), 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (0.110g, 0.47mmol) and *p*-TSA (cat.) in CH_3CN (1ml) were heated in a sealed vessel at 160°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated. The residue was purified by column chromatography using Biotage 25M cartridge, with *iso*-hexane / EtOAc (15-80%) as eluant, to give the title compound (135mg, 55%).
LC/MS t=3.80 min [MH^+] 517.

b) 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid



3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (0.135g, 0.26mmol) was dissolved in ethanol (2ml) and 2M NaOH (0.5ml) and was heated in a sealed vessel at 120°C for 5 minutes using microwaves. Upon cooling the reaction was diluted with CH_2Cl_2 (8ml) and shaken with dil.

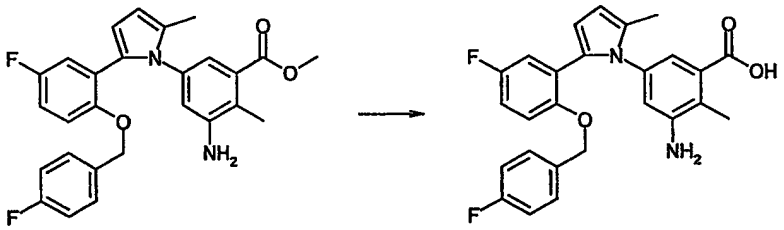
HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated to give the title compound (98mg, 75%).
^{1}H-NMR (400MHz, *d*6-DMSO) 2.01 (2H, quin, J=7Hz), 2.10 (3H, s), 2.45-2.53 (2H excess, m), 3.61-3.67 (2H, m), 4.77 (2H, s), 6.08 (1H, d, J=3Hz), 6.25 (1H, d, J=3Hz), 6.86 (1H, dd, J=4.5, 9Hz), 6.91-7.03 (2H, m), 7.10-7.20 (4H, m), 7.23 (1H, s), 7.56-7.59 (1H, m), 8.16 (1H, s).
LC/MS t=3.65 min [MH^+] 503.

Example 234 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid

a) 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid methyl ester

1-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.15g, 0.47mmol), 3,5-diamino-2-methyl-benzoic acid methyl ester (0.085g, 0.47mmol) and *p*-TSA (cat.) in CH_3CN (1ml) were heated in a sealed vessel at 160°C for 10 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated. The residue was purified by column chromatography using Biotage 25M cartridge, with *iso*-hexane / EtOAc (7-50%) as eluant, to give the title compound (125mg, 57%).
LC/MS t=3.81 min [MH^+] 463.

b) 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid



3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid methyl ester (0.125g, 0.27mmol) was dissolved in ethanol (2ml) and 2M NaOH (0.5ml) and was heated in a sealed vessel at 120°C for 5 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (8ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated to give the title compound (115mg, 95%).
^{1}H-NMR (400MHz, *d*6-DMSO) 2.05 (3H, s), 2.20 (3H, s), 4.90 (2H, s), 6.00 (1H, d, J=3.5Hz), 6.23 (1H, d, J=3.5Hz), 6.58 (1H, s), 6.69 (1H, s), 6.78 (1H, dd, J=3, 9Hz), 6.86-6.98 (2H, m), 7.12-7.19 (2H, m), 7.23-7.29 (2H, m).
LC/MS t=3.60 min [MH^+] 449.

Example 235 3-{2-[5-Fluoro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid

a) 5-Fluoro-2-(2,4-difluoro-benzyloxy)-benzaldehyde

5-Fluorosalicylaldehyde (5.0g, 35.7mmol), 2,4-difluorobenzyl bromide (4.62ml, 35.7mmol) and K_2CO_3 (4.9g, 35.7mmol) were heated in DMF (50ml) at 50°C for 30mins. Upon cooling to room temperature, EtOAc and sat. NH_4Cl were added. The layers were separated and the aqueous phase was extracted with EtOAc (x2). The combined organic extracts were washed with water, dried ($MgSO_4$), filtered and concentrated to give the title compound (9.3g, 98%).

^{1}H NMR (400MHz, $CDCl_3$) 5.19 (2H, s), 6.85-6.97 (2H, m), 7.06 (1H, dd, J=4, 9Hz), 7.23-7.30 (1H excess, m), 7.42-7.50 (2H, m), 7.53 (1H, dd, J=3.5, 8Hz), 10.45 (1H, s).

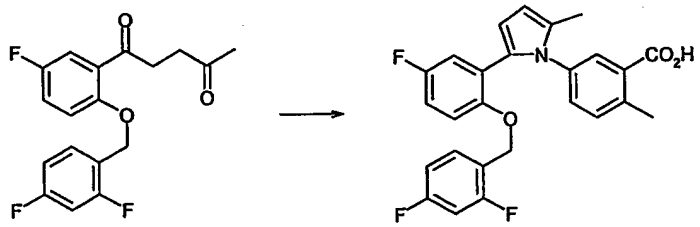
LC/MS t=3.48 min.

b) 1-[5-Fluoro-2-(2,4-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione

A mixture of 5-Fluoro-2-(2,4-difluoro-benzyloxy)-benzaldehyde (9.3g, 35mmol), methyl vinyl ketone (2.92ml, 35mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (2.48g, 9.8mmol) and triethylamine (14.5ml, 105mmol) was heated in ethanol (8ml) at 80°C for 16 hours. Upon cooling, the mixture was diluted with EtOAc (100ml) and washed with saturated NH_4Cl, brine, dried (Na_2SO_4) filtered and concentrated. The residue was purified by chromatography using Biotage with *iso*-hexane containing a gradient of EtOAc (5-20%) to give the title compound as an oil (7.36g, 63%).

LC/MS t=3.40 min [MNa^+] 359.

c) 3-{2-[5-Fluoro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid



1-[5-Fluoro-2-(2,4-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.15g, 0.44mmol), 5-amino-2-methyl-benzoic acid (0.067g, 0.44mmol) and *p*-TSA (cat.) in CH_3CN (1ml) were heated in a sealed vessel at 160°C for 10 minutes using microwaves. Upon cooling the reaction was diluted with CH_2Cl_2 (5ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a Na_2SO_4 cartridge attached and concentrated. The residue was purified by chromatography, with *iso*-hexane / EtOAc (10-30%) as eluant, to give the title compound (82mg, 41%).

^{1}H-NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 2.62 (3H, s), 4.76 (2H, s), 6.12 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.65 (1H, dd, J=4, 9Hz), 6.73-6.85 (3H, m), 6.92 (1H, dd, J=3, 9Hz), 6.99-7.14 (3H, m), 7.74 (1H, d, J=2Hz).

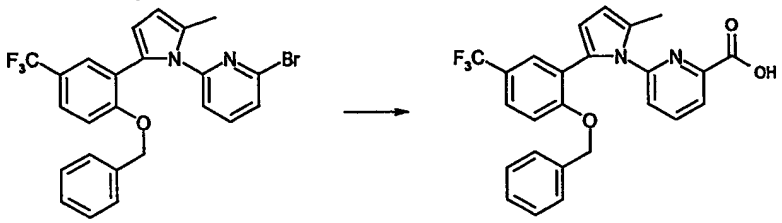
LC/MS t=4.01 min [MH^+] 452.

Example 236 6-{2-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid

a) 6-{2-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-2-bromo-pyridine

1-[5-trifluoromethyl-2-(benzyloxy)-phenyl]-pentane-1,4-dione (1.5g, 4.3mmol), 2-amino-6-bromopyridine (0.75g, 4.3mmol) and *p*-TSA (10mg, cat.) in CH_3CN (5ml) were heated in a sealed vessel at 200°C for 1.5 hours using microwaves. Upon cooling the reaction was concentrated and the residue was purified by chromatography on silica gelwith *iso*-hexane / EtOAc (5%) as eluant, to give the title compound (645mg, 31%).
LC/MS t = 4.14 min [MH^+] 487/489.

b) 6-{2-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid



n-Butyl lithium (1.6M in hexanes, 0.94ml, 1.5mmol) was added to 6-[2-(5-trifluoromethyl-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-2-bromo-pyridine (0.49g, 1mmol) in THF (15ml) at -78°C. After 50 minutes at this temperature, solid CO_2 was added and the solution warmed to room temperature. The solution was concentrated *in vacuo* and the residue triturated with *iso*-hexane/2% EtOAc. The off white solid was filtered, washed with further *iso*-hexane and air dried to give the title compound (0.38g, 84%).
^{1}H NMR (400MHz, *d*6-DMSO) 2.15 (3H, s), 5.08 (2H, s), 6.05 (1H, d, J=3Hz), 6.41 (1H, d, J=3Hz), 6.77 (1H, d, J=8Hz), 7.04 (1H, d, J=2Hz), 7.11 (1H, d, J=8Hz), 7.28-7.43 (6H, m), 7.67 (1H, t, J=8Hz), 7.81 (1H, d, J=8Hz).
LC/MS t=3.88 min [MH^+] 453.

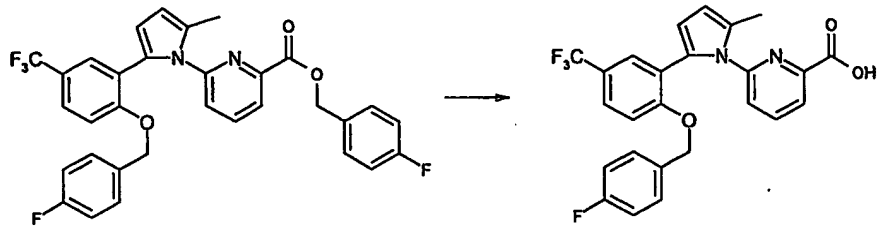
<u>Example 237 6-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic-acid</u>

a) 6-{2-[5-Trifluoromethyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid
6-{2-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid (0.38g, 0.84mmol), ammonium formate (0.265mg, 4.2mmol) and 10% Pd/C (50% wet, 0.080g, ~0.04mmol) were heated in ethanol (5ml) at 60°C for 1 hour. The mixture was cooled, filtered through Celite®, washing through with EtOAc. The solution was concentrated *in vacuo* to give the title compound (0.42g).
LC/MS t=3.64 min [MH^+] 363.

b) 6-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic-acid-(4-fluoro-benzyl)-ester
6-{2-[5-Trifluoromethyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid (0.10g, 0.28mmol), 4-fluorobenzyl bromide (0.070ml, 0.56mmol) and K_2CO_3 (0.85g, 0.61mmol) were heated in DMF (1.2ml) at 60°C for 16 hours. Further 4-fluorobenzyl bromide (0.070ml, 0.56mmol) was added and heating continued for a further 24 hours. The mixture was cooled, diluted with CH_2Cl_2 (5ml) and shaken with water (1ml). The organics were separated using a phase separator column with a Na_2SO_4 cartridge attached and concentrated. The residue was purified by chromatography on silica gel, with *iso*-hexane / EtOAc (10-15%) as eluant, to give the title compound (70mg, 44%).

LC/MS t=4.19 min [MH^+] 579.

c) 6-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic-acid



6-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic-acid-(4-fluoro-benzyl)-ester (0.07g, 0.12mmol) was dissolved in ethanol (4ml) and 2M NaOH (1ml) and was heated in a sealed vessel at 120°C for 15 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (10ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a Na_2SO_4 cartridge attached and concentrated. The residue was triturated with *iso*-hexane/2% EtOAc. The off white solid was filtered, washed with further *iso*-hexane and air dried to give the title compound (45mg).

^1H NMR (400MHz, $CDCl_3$) 2.31 (3H, s), 4.61 (2H, s), 6.20 (1H, d, J=3.5Hz), 6.38 (1H, d, J=3.5Hz), 6.77 (1H, d, J=8Hz), 7.01 (4H, d, J=8Hz), 7.05 (1H, d, J=8Hz), 7.47 (1H, dd, J=2, 8Hz), 7.61 (1H, d, J=2Hz), 7.75 (1H, t, J=8Hz), 8.01 (1H, d, J=8Hz).

LC/MS t=3.87 [MH^+] 471.

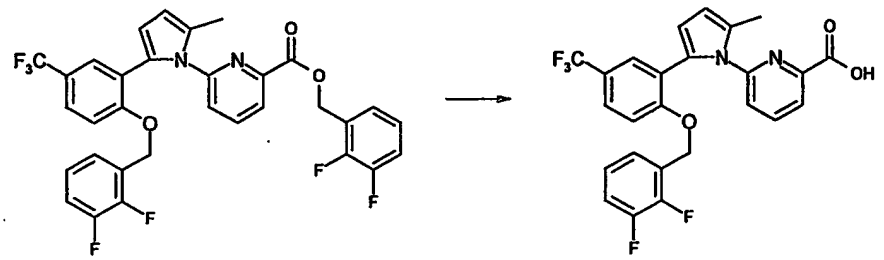
<u>Example 238 6-{2-[5-Trifluoromethyl-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic-acid</u>

a) 6-{2-[5-Trifluoromethyl-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic-acid-(2,3-difluoro-benzyl)-ester

6-{2-[5-Trifluoromethyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid (0.10g, 0.28mmol), 2,3-difluorobenzyl bromide (0.072ml, 0.56mmol) and K_2CO_3 (0.85g, 0.61mmol) were heated in DMF (1.2ml) at 60°C for 16 hours. Further 2,3-difluorobenzyl bromide (0.072ml, 0.56mmol) was added and heating continued for a further 24 hours. The mixture was cooled, diluted with CH_2Cl_2 (5ml) and shaken with water (1ml). The organics were separated using a phase separator column with a Na_2SO_4 cartridge attached and concentrated. The residue was purified by chromatography on silica gel, with *iso*-hexane / EtOAc (15%) as eluant, to give the title compound (40mg, 24%).

LC/MS t=4.21 min [MH^+] 615.

b) 6-{2-[5-Trifluoromethyl-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic-acid



6-{2-[5-Trifluoromethyl-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic-acid-(2,3-difluoro-benzyl)-ester (0.04g, 0.07mmol) was dissolved in ethanol (4ml) and 2M NaOH (1ml) and was heated in a sealed vessel at 120°C for 15 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (10ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated. The residue was triturated with *iso*-hexane/2% EtOAc. The off white solid was filtered, washed with further *iso*-hexane and air dried to give the title compound (25mg).

^{1}H NMR (400MHz, *d*6-DMSO) 2.20 (3H, s), 5.04 (2H, s), 6.08 (1H, d, J=3Hz), 6.35 (1H, d, J=3Hz), 7.00-7.08 (2H, m), 7.14-7.23 (3H, m), 7.36-7.46 (1H, m), 7.52 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz).

LC/MS t=3.88 min [MH^+] 489.

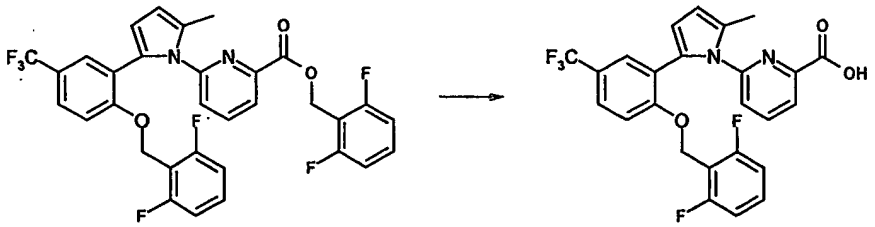
Example 239 6-{2-[5-Trifluoromethyl-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic-acid

a) 6-{2-[5-Trifluoromethyl-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic-acid-(2,6-difluoro-benzyl)-ester

6-{2-[5-Trifluoromethyl-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid (0.10g, 0.28mmol), 2,6-difluorobenzyl bromide (0.15g, 0.56mmol) and K_2CO_3 (0.85g, 0.61mmol) were heated in DMF (1.2ml) at 60°C for 16 hours. Further 2,6-difluorobenzyl bromide (0.15g, 0.56mmol) was added and heating continued for a further 24 hours. The mixture was cooled, diluted with CH_2Cl_2 (5ml) and shaken with water (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated. The residue was purified by chromatography on silica gel, with *iso*-hexane / EtOAc (15%) as eluant, to give the title compound (75mg, 44%).

LC/MS t=4.15 min [MH^+] 615.

b) 6-{2-[5-Trifluoromethyl-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic-acid



6-{2-[5-Trifluoromethyl-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic-acid-(2,6-difluoro-benzyl)-ester (0.07g, 0.11mmol) was dissolved in ethanol (4ml) and 2M NaOH (1ml) and was heated in a sealed vessel at 120°C for 15 minutes using a microwave. Upon cooling the reaction was diluted with CH_2Cl_2 (10ml) and shaken with dil. HCl (1ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated. The residue was triturated with *iso*-hexane/2% EtOAc. The off white solid was filtered, washed with further *iso*-hexane and air dried to give the title compound (22mg).

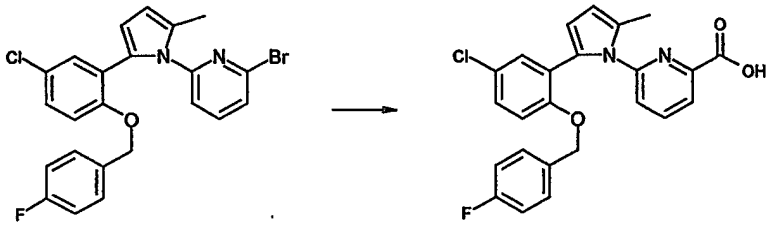
^{1}H NMR (400MHz, $CDCl_3$) 2.27 (3H, s), 4.79 (2H, s), 6.12 (1H, s), 6.32 (1H, d, J=3Hz), 6.84-7.06 (4H, m), 7.27-7.38 (1H, m), 7.47-7.55 (2H, m), 7.73-7.79 (1H, m), 8.01 (1H, d, J=7Hz).
LC/MS t=3.81 min [MH^+] 489.

Example 240 6-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid

a) 6-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-2-bromo-pyridine

1-[5-Chloro-2-(4-fluorobenzyloxy)-phenyl]-pentane-1,4-dione (2.05g, 6.1mmol), 2-amino-6-bromopyridine (1.06g, 6.1mmol) and *p*-TSA (10mg, cat.) in CH_3CN (5ml) were heated in a sealed vessel at 200°C for 2 hours usinga microwave. Upon cooling the reaction was concentrated and the residue was purified by chromatography on silica gel with *iso-hexane* / EtOAc (1-10%) as eluant, to give the title compound (550mg, 19%).
LC/MS t = 4.15 min [MH^+] 471/473/475.

b) 6-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid



n-Butyl lithium (1.6M in hexanes, 0.94ml, 1.5mmol) was added to 6-{2-[5-chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-2-bromo-pyridine (0.55g, 1.17mmol) in THF (15ml) at -78°C. After 1 hour at this temperature, solid CO_2 was added and the solution warmed to room temperature. The solution was concentrated *in vacuo* and the residue was purified by MDAP to give the title compound (60mg).
^{1}H NMR (400MHz, $CDCl_3$) 2.32 (3H, s), 4.51 (2H, s), 6.18 (1H, d, J=3.5Hz), 6.33 (1H, d, J=3.5Hz), 6.62 (1H, d, J=9Hz), 6.98 (4H, d, J=7Hz), 7.04 (1H, d, J=8Hz), 7.16 (1H, dd, J=2.5, 8Hz), 7.37 (1H, d, J=2.5Hz), 7.74 (1H, t, J=8Hz), 8.00 (1H, d, J=8Hz).
LC/MS t=3.91 min [MH^+] 437/439.

Example 241 6-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid

a) 6-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-2-bromo-pyridine

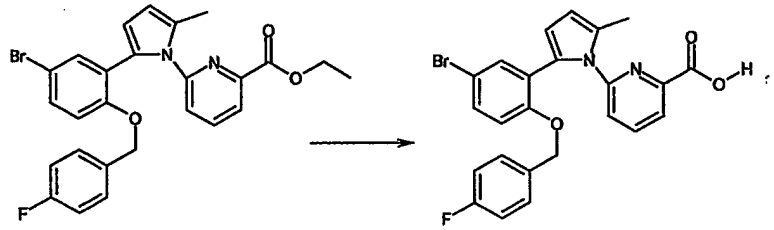
Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-6-chloro-benzoic acid using the appropriate amine.
LC/MS t=4.25 min [MH+] 515/517/519.

b) 6-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester

6-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-2-bromo pyridine (0.10g, 0.194mmol, 1eq) was dissolved in ethanol (2ml) and

bis(triphenylphosphine)palladium(II)chloride (0.0048g, 0.0068mmol, 0.035eq), and triethylamine (0.6ml) were added, and the solution saturated with $CO_{(g)}$ for 10 min with stirring. The reaction was heated to 70°C with stirring under $CO_{(g)}$ for 28 hours, and bis(triphenylphosphine)palladium(II)chloride (0.0048g, 0.0068mmol, 0.035eq), and triethylamine (0.6ml) were added, the solution was re-saturated with $CO_{(g)}$ for 10 mins and heated to 70°C for a further 18 hours. The reaction mixture was diluted with EtOAc, and washed with water, the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the volatiles were removed *in vacuo*. The residue was then purified by chromatography using Biotage Flash 12+S cartridge with 5% EtOAc:*iso*-hexane as the eluant to yield the title compound (0.056g, 0.11mmol, 57%) as a yellow solid.
LC/MS t=4.10 min [MH+] 509/511.

c) 6-{2-[5-Bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid



Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-5-(1,1-dioxo-1l^6-isothiazolidin-2-yl)-benzoic acid.
^{1}H NMR (400MHz, $CDCl_3$) 2.30 (3H, s), 4.51 (2H, s), 6.17 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.57 (1H, d, J=8Hz), 6.98 (4H, d, J=8Hz), 7.03 (1H, d, J=8Hz), 7.29 (1H, dd J=8Hz, 2Hz), 7.50, (1H, d, J=2Hz), 7.73 (1H, t, J=8Hz), 8.00 (1H, d, J=8Hz).
LC/MS t=4.15 min [MH+] 481/483.

Example 242 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid

a) 2-(4-Fluoro-benzyloxy)-5-trifluoromethyl-benzaldehyde

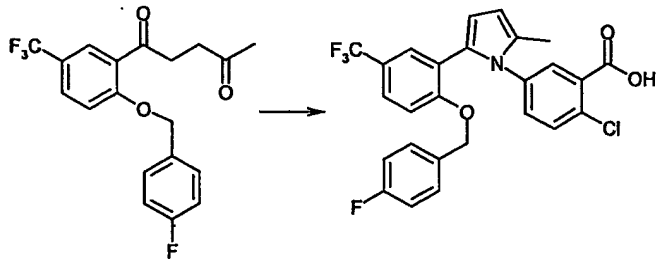
2-Hydroxy-5-trifluoromethyl-benzaldehyde (10.00g, 0.053mol, 1eq) was added to DMF (100ml), K_2CO_3 (14.53g, 0.105mol, 2eq) and p-fluorobenzylbromide (9.95g, 0.053mol, 1eq) were then added to the stirred reaction mixture. The reaction was stirred at room temperature for 1 hour. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the volatiles were removed *in vacuo* to yield title compound (13.00g, 0.044mol, 82%) as a dark orange oil.
LC/MS t=3.46.

b) 1-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione

2-(4-Fluorobenzyloxy)-5-trifluoromethyl-benzaldehyde (14.00g, 0.047mol, 1eq) was dissolved in ethanol (7ml) and methylvinylketone (3.98g, 0.047mol, 1.02eq), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (3.551g, 0.014mol, 0.3eq) and Et_3N (14.23g, 0.141mol, 3eq) were added to the stirred reaction mixture. The vessel was heated at reflux and stirred in a nitrogen atmosphere for 18 hours. The reaction mixture was quenched with sat. NH_4Cl solution and extracted with EtOAc, the combined organic extracts were

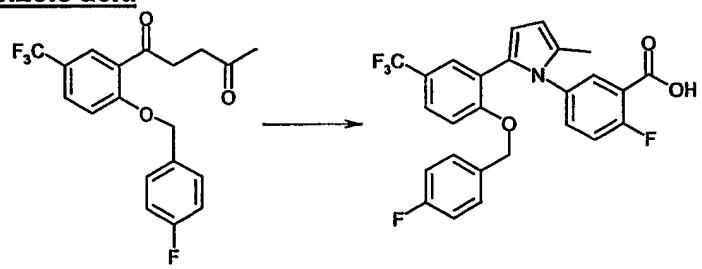
washed with brine, dried (MgSO4), filtered and the volatiles were removed *in vacuo*. The residue was then purified by chromatography on silica gel with 10% EtOAc:*iso*-hexane as the eluant to yield the title compound (9.17g, 0.025mol, 53%) as an off-white solid.
LC/MS t=3.58 min [MH-] 367.

c) 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid



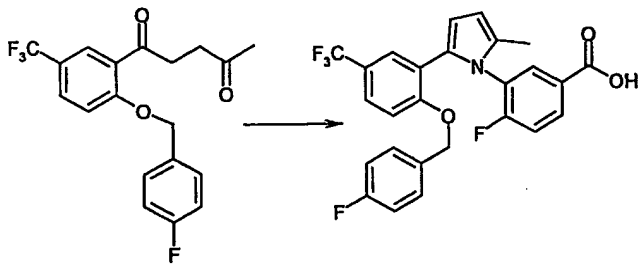
1-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.200g, 0.54mmol, 1.00eq) and pTSA (0.0305g, 0.16mmol, 0.30eq) were heated in a sealed vessel with stirring, at 150°C for 540 seconds. The reaction mixture was allowed to warm to room temperature and the reaction mixture was diluted with ether, washed with 2M HCl solution and 2M sodium bicarbonate solution. The combined organic extracts were washed with brine and dried ($MgSO_4$), filtered and volatiles removed *in vacuo*. The residue was purified by chromatography on silica gel with 20% EtOAc:*iso*-hexane as the eluant to yield the title compound (0.122g, 45%) as yellow solid.
^{1}H NMR (400MHz, *d*6-DMSO) 2.09 (3H, s), 4.96 (2H, s), 6.09 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 7.06 (1H, d, J=8Hz), 7.13-7.24 (5H, m), 7.38 (1H, d, J=2Hz), 7.41 (1H, d, J=3Hz), 7.48 (1H, d, J=9Hz), 7.54 (1H, dd, J=9Hz, 2Hz), 13.55 (1H, s).
LC/MS t=4.15 min [MH+] 504/506.

Example 243 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid



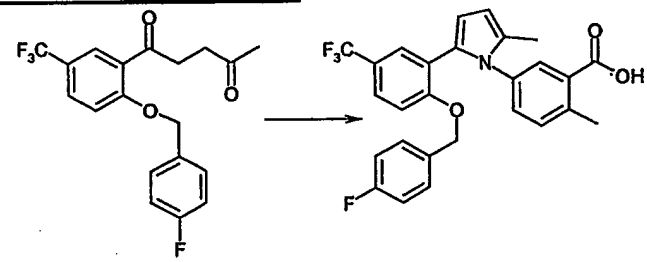
Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.
^{1}H NMR (400MHz, *d*6-DMSO) 2.08 (3H, s), 4.98 (2H, s), 6.08 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 7.08 (1H, d, J=8Hz), 7.15-7.21 (2H, m), 7.23-7.35 (5H, m) 7.42-7.45 (1H, m), 7.53 (1H, dd, J=9Hz, 2Hz),13.35 (1H, s).
LC/MS t=4.01 min [MH+] 488.

Example 244 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-4-fluoro-benzoic acid



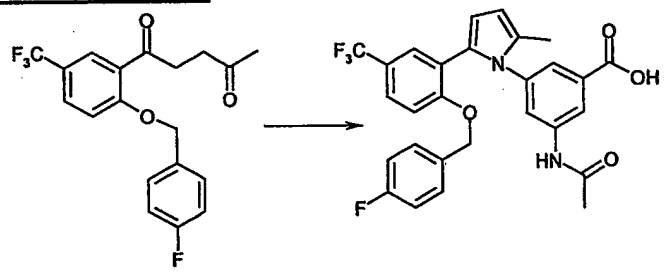
Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.
LC/MS t=4.01 min [MH+] 488.

Example 245 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester



Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.
^{1}H NMR (400MHz, *d*6-DMSO) 2.06 (3H, s), 2.49 (3H, s), 4.98 (2H, s), 6.06 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 7.05 (1H, d, J=8H), 7.10-7.32 (7H, m), 7.43 (1H, d, J=3Hz), 7.49 (1H, dd, J=8Hz, 1Hz), 12.80 (1H brs).
LC/MS t=3.84 min [MH+] 484.

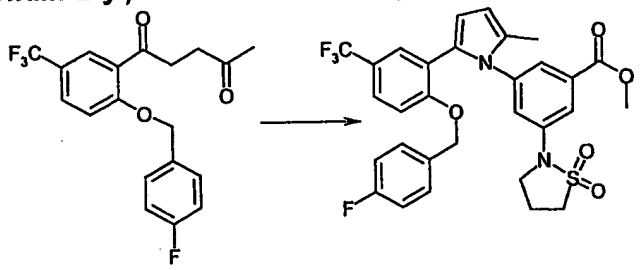
Example 246 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5- acetylamino-benzoic acid



Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.
^{1}H NMR (400MHz, $CDCl_3$) 2.09 (3H, s), 2.13 (3H, s), 4.80 (2H, s), 6.11 (1H, d, J=3Hz), 6.33 (1H, d, J=3Hz), 6.69 (1H, d, J=9Hz), 6.95 (2H, t, J=8Hz), 7.03-7.12 (2H, m) 7.28 (1H, d, J=8Hz,), 7.43 (2H, d, J=4Hz), 7.60 (1H, s), 7.96 (1H, s,), 9.7 (1H, brs).
LC/MS t=3.52 [MH+] 527.

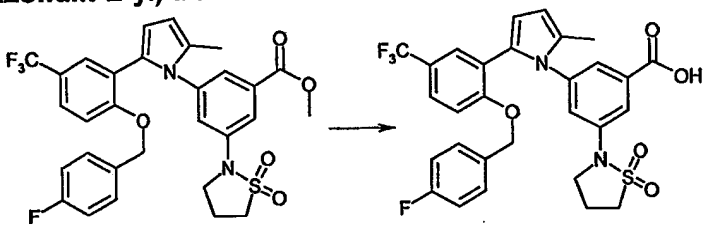
Example 247 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid

a) 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5- (1,1-Dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid methyl ester



Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.
LC/MS t=4.00 min [MH+] 603.

b) 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid



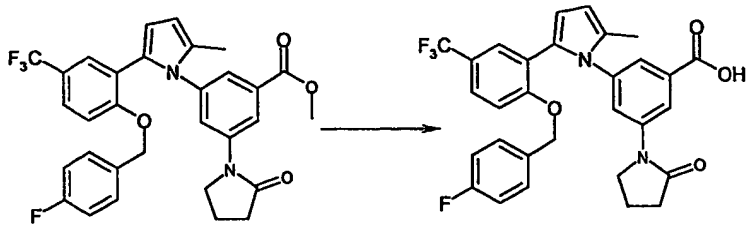
3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5- (1,1-Dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid methyl ester (0.20g, 0.33mmol, 1eq) was dissolved in ethanol (5ml) and 2M NaOH (2ml) was added. The reaction vessel was then heated with stirring to reflux for 2 hours. The reaction mixture was diluted with H_2O and extracted with ether. The aqueous extract was acidified with 2M HCl and extracted with ether and the combined organic extracts were washed with brine and dried ($MgSO_4$), filtered and the volatiles were removed *in vacuo* to yield the title compound (0.087g, 45%) as a yellow oil.
^{1}H NMR (400MHz, $CDCl_3$) 2.22 (3H, s), 2.47 (2H, quint, J=7), 3.33 (2H, t, J=7), 3.48 (2H, t, J=7), 4.81 (2H, s), 6.16 (1H, d, J=3Hz), 6.33 (1H, d, J=3Hz), 6.73 (1H, d, J=9Hz), 6.93-7.03 (3H, m), 7.50-7.11 (2H, m) 7.36 (1H, dd, J=8Hz, 2Hz), 7.48 (1H, d, J=2Hz), 7.57 (1H, t, J=1Hz) 7.84 (1H, t, J=1Hz).
LC/MS t=3.57 min [MH+] 589.

Example 248 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid

a) 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester

Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.
LC/MS t=4.02 min [MH+] 567.

b) 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid



Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid.

^{1}H NMR (400MHz, $CDCl_3$) 2.22 (3H, s), 2.47 (2H, quint, J=7), 3.33 (2H, t, J=7), 3.48 (2H, t, J=7), 4.83 (2H, s), 6.16 (1H, d, J=3Hz), 6.33 (1H, d, J=3Hz), 6.74 (1H, d, J=8H), 6.97-7.08 (3H, m), 7.23-7.34 (4H, m), 7.39 (1H, dd, J=8Hz, 1Hz), 7.54 (1H, d, J=2Hz), 7.65 (1H, d, J=2Hz).

LC/MS t=3.62 min [MH+] 553.

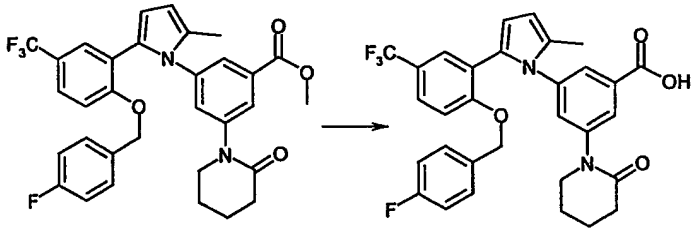
Example 249 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester

a) 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5- (2-oxo-piperidin-1-yl)-benzoic acid methyl ester

Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.

LC/MS t=3.96 min [MH+] 581.

b) 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester



Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid.

^{1}H NMR (400MHz, *d*6-DMSO) 1.73-1.81 (2H m), 2.07-2.18 (5H, m), 2.34-2.40 (2H, m), 2.48-2.53 (2H, m), 4.94 (2H, s), 6.10 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 7.05 (1H, d, J=8Hz), 7.07-7.28 (5H, m), 7.32 (1H, t, H=1), 7.41 (1H, d, J=2Hz), 7.53 (1H, dd, J=8Hz, 2Hz), 7.78 (1H, t, J=1Hz), 13.00 (1H, br s).

LC/MS t=3.56 min [MH+] 567.

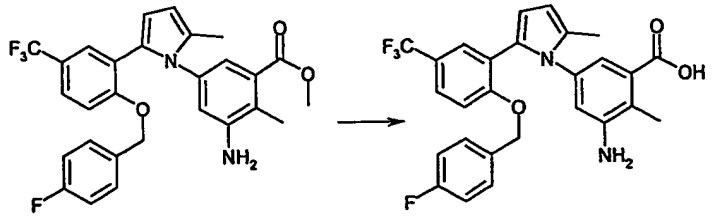
Example 250 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid methyl ester

a) 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid methyl ester

Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.

LC/MS t=3.96 min [MH+] 513.

b) 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid methyl ester

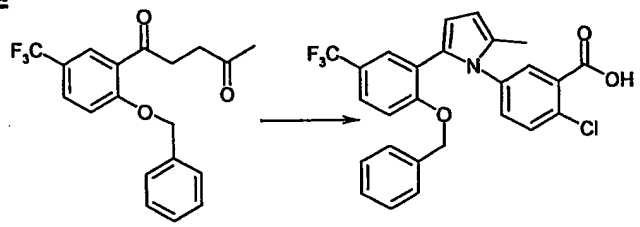


Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid.

^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 2.37 (3H, s), 3.71 (2H, s), 4.86 (2H, s), 6.11 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.42 (1H, d, J=2H), 6.74 (1H, d, J=8Hz), 6.95-7.02 (2H, m), 7.06-7.14 (3H, m), 7.35 (1H, dd, J=8Hz, 1Hz), 7.48 (1H, d, J=2Hz).

LC/MS. t=3.57 min [MH+] 499.

Example 251 3-{2-[5-Trifluoromethyl-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid

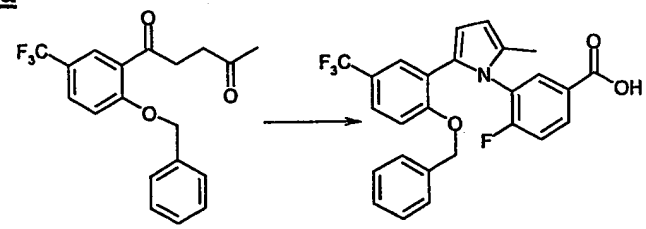


Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.

^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.83 (2H, s), 6.16 (1H, d, J=3Hz), 6.33 (1H, d, J=3Hz), 6.74 (1H, d, J=8H), 6.97-7.08 (3H, m), 7.23-7.34 (4H, m), 7.39 (1H, dd, J=8Hz, 1Hz), 7.54 (1H, d, J=2Hz), 7.65 (1H, d, J=2Hz).

LC/MS t=4.16 min [MH+] 486/488.

Example 252 3-{2-[5-Trifluoromethyl-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-4-fluoro-benzoic acid

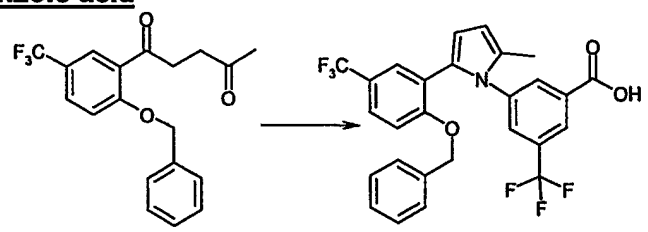


Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.

^{1}H NMR (400MHz, $CDCl_3$) 2.12(3H, s), 4.94 (2H, s), 6.18 (1H, d, J=3Hz), 6.40 (1H, d, J=3Hz), 6.72 (1H, d, J=9H), 7.07-7.15 (3H, m), 7.24-7.36 (4H, m), 7.45 (1H, d, J=2Hz), 7.82 (1H, dd, J=8Hz, 2Hz), 8.01 (1H, m).

LC/MS t=3.99 min [MH+] 470.

Example 253 3-{2-[5-Trifluoromethyl-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid



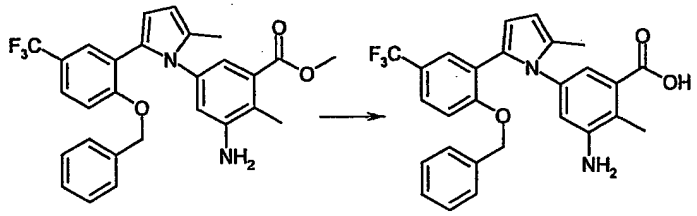
Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.
^{1}H NMR (400MHz, $CDCl_3$) 2.19 (3H, s), 4.81 (2H, s), 6.18 (1H, d, J=3Hz), 6.38 (1H, d, J=3Hz), 6.73 (1H, d, J=9H), 7.03-7.08 (2H, m), 7.24-7.32 (3H, m), 7.39 (1H, dd, J=8Hz, 1Hz), 7.44 (1H, s), 7.52 (1H, d, J=2Hz), 7.89 (1H, s), 8.17 (1H, s).
LC/MS t=4.19 min [MH+] 520.

Example 254 3-{2-[5-Trifluoromethyl-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid

a) 3-{2-[5-Trifluoromethyl-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid methyl ester

Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.
LC/MS t=4.03 min [MH+] 495.

b) 3-{2-[5-Trifluoromethyl-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6methyl-benzoic acid



Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid.
^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 2.18 (2H, s), 2.36 (3H, s), 4.98 (2H, s), 6.11 (1H, d, J=3Hz), 6.33 (1H, d, J=3Hz), 6.42 (1H, d, J=2H) 6.73 (1H, d, J=8Hz), 7.08-7.15 (3H, m), 7.25-7.36 (4H, m) 7.48 (1H, d, J=2Hz,).
LC/MS t=3.71 min [MH+] 481.

Example 255 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid

a) 2-(2,4-Difluoro-benzyloxy)-5-trifluoromethyl-benzaldehyde

Procedure as for 2-(4-Fluoro-benzyloxy)-5-trifluoromethyl-benzaldehyde using the appropriate benzyl bromide.

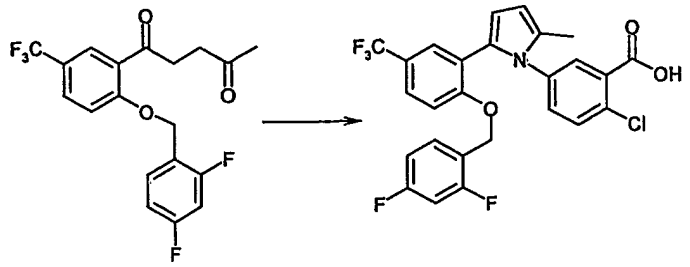
LC/MS t=3.74 min.

b) 1-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione

Procedure as for 1-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione.

LC/MS t=3.62 min [MH-] 387.

c) 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid

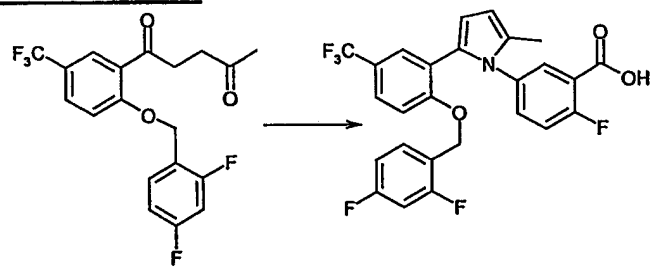


Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.

^{1}H NMR (400MHz, $CDCl_3$) 2.06 (3H, s), 4.88 (2H, s), 6.11 (1H, d, J=3Hz), 6.33 (1H, d, J=3Hz), 6.72-6.84 (3H, m), 7.08 (1H, dd, J=14Hz, 8Hz), 7.34 (1H, d, J=8Hz) 7.42 (2H, d, J=6Hz,), 7.72 (1H, s), 7.94 (1H, s), 9.80 (1H, s).

LC/MS t=3.89 min [MH+] 522/524.

Example 256 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid

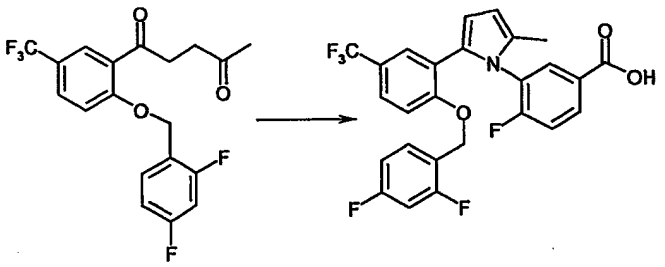


Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.

^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 4.88 (2H, s), 6.14 (1H, d, J=3Hz), 6.33 (1H, d, J=3Hz), 6.77-6.87 (3H, m), 6.98-7.16 (3H, m), 7.42 (1H, dd, J=9Hz, 2Hz) 7.48 (1H, d, J=2Hz,), 7.69 (1H, dd, J=6Hz, 3Hz), 10.30 (1H, s).

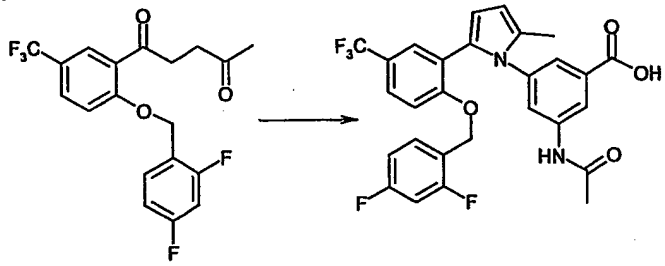
LC/MS t=3.74 min [MH+] 506.

Example 257 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-4-fluoro-benzoic acid



Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.
^{1}H NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 4.94 (2H, s), 6.17 (1H, d, J=3Hz), 6.38 (1H, d, J=3Hz), 6.75-6.85 (3H, m), 7.06-7.16 (2H, m), 7.37 (1H, dd, J=9Hz, 2Hz) 7.44 (1H, d, J=2Hz,), 7.78 (1H, dd, J=8Hz, 2Hz), 8.02 (1H, m), 9.80 (1H, br s).
LC/MS t=3.73 min [MH+] 506.

Example 258 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-acetylamino-benzoic acid



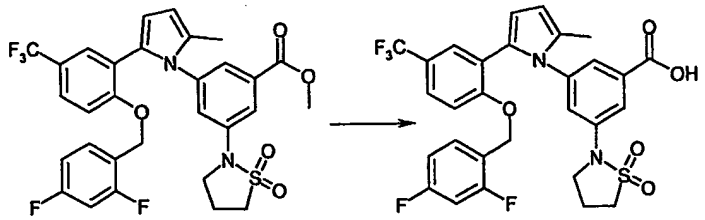
Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.
^{1}H NMR (400MHz, $CDCl_3$) 2.05 (3H, s), 2.16 (3H, s), 4.86 (2H, s), 6.15 (1H, d, J=3Hz), 6.33 (1H, d, J=3Hz), 6.74-6.88 (3H, m), 6.95-7.05 (2H, m), 7.32 (1H, d, J=8Hz) 7.43 (1H, dd, J=9Hz 2Hz,), 7.53 (1H, s), 7.68 (1H, d, J=3Hz), 10.60 (1H, s).
LC/MS t=3.53 min [MH+] 545.

Example 259 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5- (1,1-dioxo-*1l^6-isothiazolidin*-2-yl)-benzoic acid

a) 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-Dioxo-*1l^6-isothiazolidin*-2-yl)-benzoic acid methyl ester

Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.
LC/MS t=3.96 min [MH+] 621.

b) 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-*1l^6-isothiazolidin*-2-yl)-benzoic acid



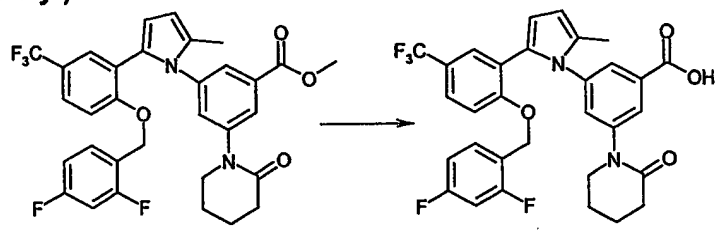
Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid using the appropriate amine.
^{1}H NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 2.46 (2H, m), 3.32 (2H, t, J=8Hz), 3.56 (2H, t, J=8Hz), 4.86 (2H, s), 6.14 (1H, d, J=3Hz), 6.34 (1H, d, J=3Hz), 6.74-6.84 (3H, m), 7.02 (1H, dd, J=16Hz, 8Hz), 7.14 (1H, t, J=1Hz), 7.40 (1H, dd J=9Hz, 2Hz), 7.45, (1H, s), 7.52 (1H, dd, J=9Hz, 2Hz), 7.69 (1H, dd, J=2Hz, 1Hz), 10.80 (1H, br s).
LC/MS t=3.58 min [MH+] 507.

Example 260 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5- (2-oxo-piperidin-1-yl)-benzoic acid

a) 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester

Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.
LC/MS t=3.93 min [MH+] 599.

b) 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid



Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid.
^{1}H NMR (400MHz, $CDCl_3$) 1.80-1.90 (2H, m), 2.02-2.10 (2H, m), 2.21 (3H, s), 2.51-2.58 (2H, m), 3.25-3.32 (2H, m), 4.85 (2H, s), 6.12 (1H, d, J=3Hz), 6.34 (1H, d, J=3Hz), 6.76-6.87 (3H, m), 7.06-7.12 (2H, m), 7.40 (1H, dd, J=8Hz, 2Hz), 7.48 (1H, d, J=2Hz), 7.58 (1H, t, J=1Hz), 7.84 (1H, t, J=1Hz), 11.25 (1H, br s).
LC/MS t=3.59 min [MH+] 585.

Example 261 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(methanesulfonyl)-benzoic acid

a) 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester

Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.

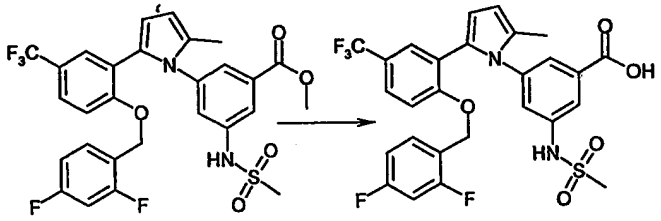
LC/MS t= 3.97 min [MH+] 517.

b) 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(methanesulfonyl)-benzoic acid methyl ester

3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5- amino-benzoic acid methyl ester (0.0222g, 0.43mmol, 1eq), was dissolved in DCM (5ml) and pyridine (0.0636g, 0.86mmol, 2eq), 4-(dimethylamino) pyridine (0.057g, 0.47mmol, 1.1eq) and methylsulfonylchloride (0.0337g, 0.29mmol, 0.7eq) were added. The reaction vessel was stirred for 18 hours at 21°C. The reaction mixture was diluted with DCM and washed with water. The combined organic extracts were washed with brine, dried (MgSO4), filtered and the volatiles were removed *in vacuo* to yield title compound (0.22g, 0.37mmol, 86%) as a pale yellow solid.

LC/MS t= 3.72 min [MH+] 595.

c) 3-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(methanesulfonyl)-benzoic acid



Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid.

^{1}H NMR (400MHz, *d*6-DMSO) 2.10 (3H, s), 2.70 (3H, s), 5.00 (2H, s), 6.08 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 7.20-7.80 (2H, m), 7.16-7.29 (5H, m), 7.53 (1H, dd, J=8Hz, 2Hz), 7.68 (1H, t, J=1Hz), 10.00 (1H, s) 13.20 (1H, s).

LC/MS t=3.61 min [MH+] 581

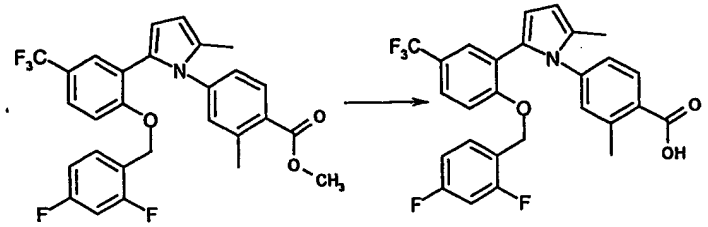
Example 262 4-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-2-methyl -benzoic acid

a) 4-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-2-methyl-benzoic acid methyl ester

Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.

LC/MS t=3.84 min [MH+] 532.

b) 4-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-2-methyl -benzoic acid



Procedure as for 3-{2-[5-Trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid.

LC/MS t=3.90 min [MH+] 518.

Example 263 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-hydroxy-benzoic acid

a) 5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-benzaldehyde

5-Chlorosalicylaldehyde (5g, 32.05mmol), 4-bromo-2-fluorobenzyl bromide (12.9g, 48.07mmol) and K_2CO_3 (8.86g, 64.1mmol) were heated in DMF (35ml, 1M) at 60°C for 3hrs. Upon cooling to room temperature, Et_2O and H_2O were added. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the title compound (6.6g, 60%).

^1H NMR (400MHz, $CDCl_3$) 5.20 (2H, s), 7.03 (1H, d, J=9Hz), 7.31-7.39 (3H, m), 7.51 (1H, dd, J=2.5Hz, J=8.8Hz), 7.82 (1H, d, J=2.5Hz), 10.43 (1H, s).

b) 1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione

A mixture of 5-chloro-2-(4-bromo-2-fluoro-benzyloxy)-benzaldehyde (3.95g, 11.50mmol), methyl vinyl ketone (1.2ml, 14.38mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (435mg, 1.725mmol, 0.15eq) and triethylamine (2.81ml, 20.125mmol) was heated in EtOH (3.83ml, 3M) at reflux for 7 hours. Upon cooling, the mixture was diluted with EtOAc and washed with sat. NH_4Cl and sat. $NaHCO_3$, dried (Na_2SO_4) filtered and concentrated. The residue was purified by chromatography, using Biotage , with cyclohexane containing a gradient of EtOAc (7.5-12.5%) to give the title compound (2.1g, 44%).

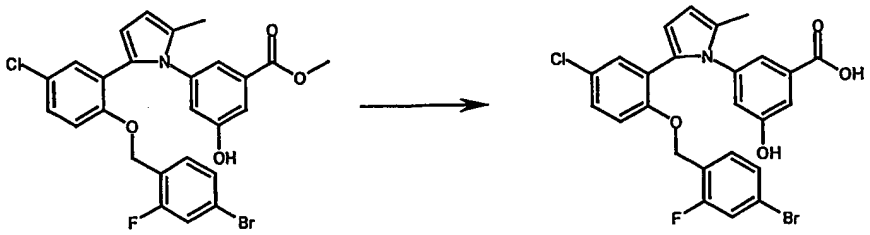
^1H NMR (400MHz, $CDCl_3$) 2.21 (3H, s), 2.79-2.82 (2H, m), 3.18-3.21 (2H, m), 5.17 (2H, s), 6.97 (1H, d, J=9.0Hz), 7.31-7.43 (4H, m), 7.70 (1H, d, J=2.8 Hz).

c) 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-hydroxy-benzoic acid methyl ester

1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.363mmol), 3-amino-5-hydroxybenzoic acid methyl ester (61mg, 0.363mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (112mg, 57%).

^1H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 3.85 (3H, s), 4.77 (2H, s), 6.12 (1H, d, J=3.3Hz), 6.29 (1H, d, J=3.5Hz), 6.61-6.63 (2H, m), 6.93 (1H, t, J=7.8Hz), 7.09 (1H, dd, J=2.8Hz, J=8.8Hz), 7.21-7.23 (3H, m), 7.31 (1H, s), 7.39 (1H, s).

d) 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-hydroxy-benzoic acid

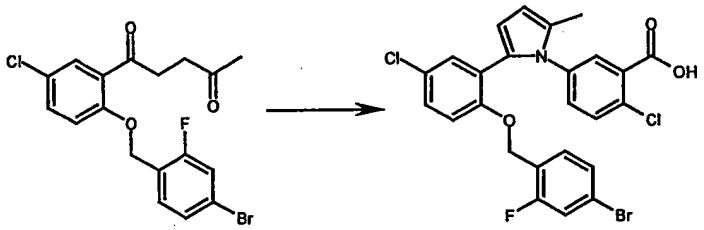


3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-hydroxy-benzoic acid methyl ester (112mg, 0.21mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (57mg, 51%).

^{1}H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.78 (2H, s), 6.13 (1H, d, J=3.3Hz), 6.30 (1H, d, J=3.3Hz), 6.63 (1H, d, J=8.8Hz), 6.69 (1H, bt, J=1.5Hz), 6.94 (1H, t, J=8.0Hz), 7.09 (1H, dd, J=2.5Hz, J=8.8Hz), 7.19-7.23 (3H, m), 7.37 (1H, s), 7.44 (1H, s).

LC/MS t=3.94 min, [MH+] 532 and 534, [MH-] 530 and 532.

Example 264 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid

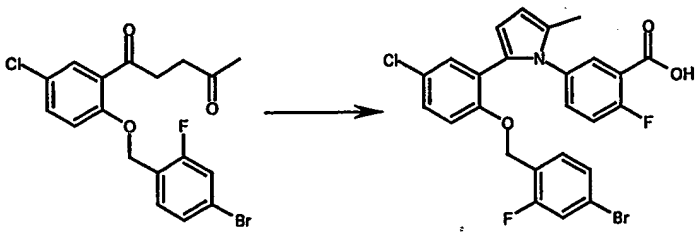


1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.363mmol), 3-amino-6-chlorobenzoic acid (62.3mg, 0.363mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (94mg, 47%).

^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.76 (2H, s), 6.14 (1H, s), 6.28 (1H, s), 6.62 (1H, d, J=9.0Hz), 6.81-6.87 (1H, m), 7.03 (1H, d, J=8.5Hz), 7.13 (1H, d, J=8.0Hz), 7.20-7.29 (3H, m's excess), 7.33 (1H, d, J=8.5Hz), 7.67 (1H, s).

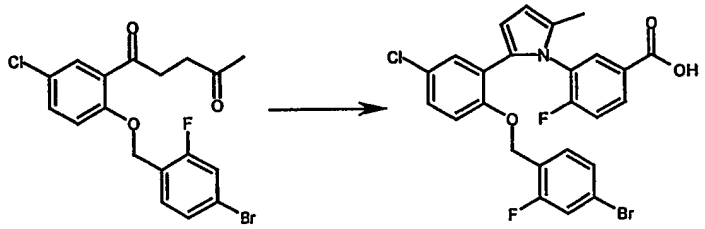
LC/MS t=4.37 min, [MH+] 550 and 552, [MH-] 548 and 550.

Example 265 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid



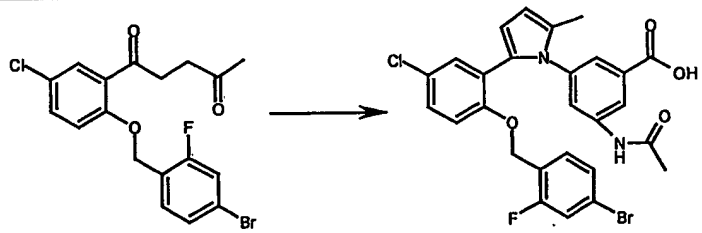
1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.363mmol), 3-amino-6-fluorobenzoic acid (56.3mg, 0.363mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (81mg, 42%).
^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 4.77 (2H, s), 6.14 (1H, s), 6.27 (1H, d, J=2.0Hz), 6.63 (1H, d, J=8.8Hz), 6.89-6.95 (1H, m), 6.99-7.06 (1H, m), 7.09-7.17 (2H, m), 7.21-7.27 (3H, m's excess), 7.69 (1H, d, J=5.8Hz).
LC/MS t=4.14 min, [MH+] 534 and 536, [MH-] 532 and 534.

Example 266 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-4-fluoro-benzoic acid



1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.363mmol), 3-amino-4-fluorobenzoic acid (56.3mg, 0.363mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (77mg, 40%).
^{1}H NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 4.84 (2H, s), 6.17 (1H, s), 6.32 (1H, d, J=2.5Hz), 6.59 (1H, d, J=8.5Hz), 6.91-6.98 (1H, m), 7.04-7.10 (1H, m), 7.11-7.19 (1H, m), 7.19-7.24 (3H, m), 7.79 (1H, d, J=7.3Hz), 8.00-8.06 (1H, m).

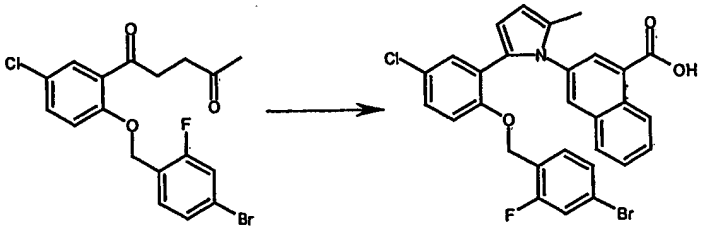
Example 267 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-acetylamino-benzoic acid



1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.363mmol), 3-amino-5-acetylaminobenzoic acid (70.5mg, 0.363mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (30-50%) to give the title compound (66mg, 32%).

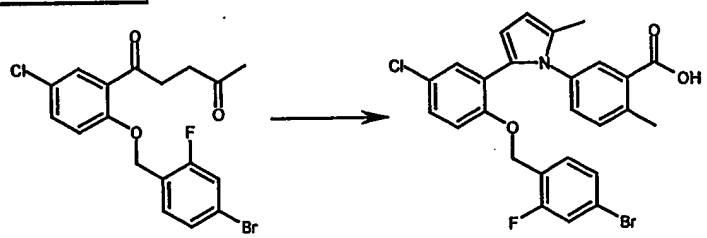
^{1}H NMR (400MHz, $CDCl_3$) 2.18 (6H, s), 4.79 (2H, s), 6.13 (1H, s), 6.29 (1H, s), 6.60 (1H, d, J=9.0Hz), 6.91-6.98 (1H, m), 7.07 (1H, d, J=8.5Hz), 7.14-7.24 (3H, m), 7.47 (1H, s), 7.62 (1H, s), 7.95 (1H, s).
LC/MS t=3.82 min, [MH+] 573 and 575, [MH-] 571 and 573.

Example 268 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-1-naphthoic acid



1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.363mmol), 3-amino-1-naphthoic acid (67.9mg, 0.363mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (98mg, 48%).
^{1}H NMR (400MHz, $CDCl_3$) 2.21 (3H, s), 4.69 (2H, s), 6.19 (1H, s), 6.33 (1H, s), 6.50 (1H, d, J=8.8Hz), 6.64-6.70 (1H, m), 7.00 (1H, d, J=8.0Hz), 7.06 (1H, d, J=9.0Hz), 7.17 (1H, d, J=9.5Hz), 7.38 (1H, s), 7.54 (1H, t, J=7.3Hz), 7.61-7.70 (3H, m), 8.09 (1H, s), 9.04 (1H, d, J=8.8Hz).
LC/MS t=4.30 min, [MH+] 566 and 568, [MH-] 564 and 566.

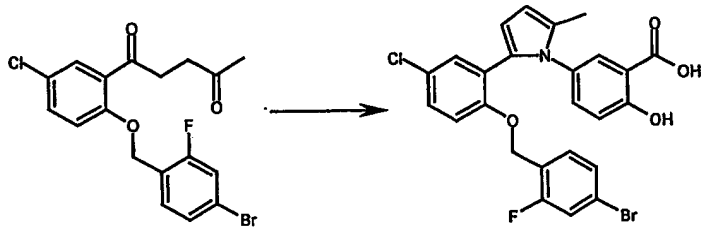
Example 269 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid



1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.363mmol), 3-amino-6-methylbenzoic acid (55mg, 0.363mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (119mg, 62%).
^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 2.63 (3H, s), 4.76 (2H, s), 6.13 (1H, d, J=3.3Hz), 6.29 (1H, d, J=3.5Hz), 6.60 (1H, d, J=8.8Hz), 6.88 (1H, t, J=7.8Hz), 7.03 (1H, dd, J=2.3Hz, J=8.0Hz), 7.06-7.15 (2H, m), 7.19 (1H, s), 7.21 (1H, s), 7.24 (1H, d, J=2.5Hz), 7.75 (1H, d, J=2.0Hz).

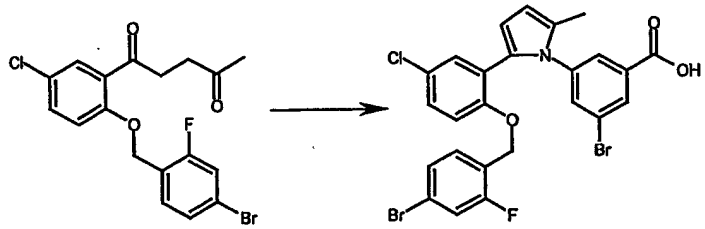
LC/MS t=4.19 min, [MH+] 530 and 532, [MH-] 528 and 530.

Example 270 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid



1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.363mmol), 3-amino-6-hydroxybenzoic acid (56mg, 0.363mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (110mg, 57%).
^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 4.82 (2H, s), 6.12 (1H, d, J=3.3Hz), 6.27 (1H, d, J=3.3Hz), 6.64 (1H, d, J=8.8Hz), 6.87 (1H, d, J=8.8Hz), 6.91-6.97 (1H, m), 7.09-7.14 (2H, m), 7.20-7.25 (3H, m), 7.56 (1H, d, J=2.5Hz), 10.34 (1H, bs).
LC/MS t=4.93 min, [MH+] 532 and 534, [MH-] 530 and 532.

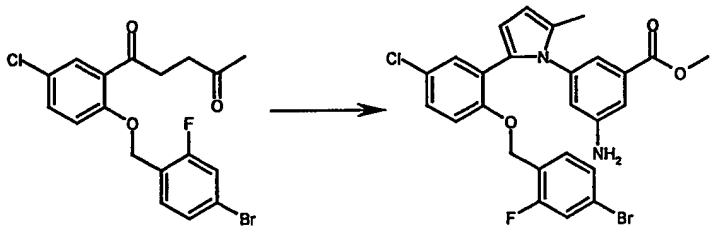
Example 271 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-bromo-benzoic acid



1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.363mmol), 3-amino-5-bromobenzoic acid (79mg, 0.363mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (45mg, 21%).
^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.76 (2H, s), 6.13 (1H, d, J=4.0Hz), 6.28 (1H, d, J=3.5Hz), 6.64 (1H, d, J=8.8Hz), 6.89-6.95 (1H, m), 7.13 (1H, dd, J=2.5Hz, J=8.8Hz), 7.24-7.28 (3H, m's excess), 7.33-7.36 (1H, m), 7.63-7.66 (1H, m), 8.09 (1H, t, J=1.5Hz).
LC/MS t=4.49 min, [MH+] 594 and 596, [MH-] 592 and 594.

Example 272 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid

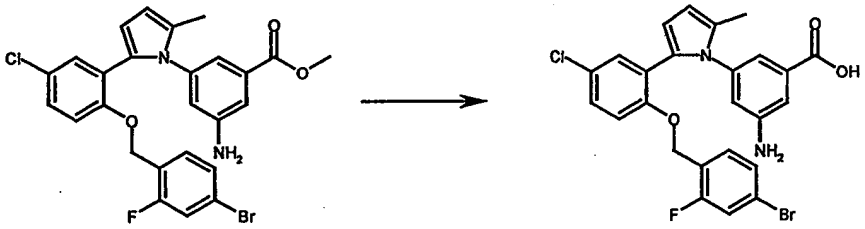
a) 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester



1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.363mmol), 3,5-diaminobenzoic acid methyl ester (60.4mg, 0.363mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (60mg, 30%).

^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 3.70 (2H, bs), 3.82 (3H, s), 4.79 (2H, s), 6.10 (1H, s), 6.29 (1H, s), 6.42 (1H, s), 6.62 (1H, d, J=8.8Hz), 6.96 (1H, t, J=7.8Hz), 7.08 (1H, d, J=8.5Hz), 7.12 (1H, s), 7.18-7.24 (4H, m).

b) 3-{2-[5-Chloro-2-(4-bromo-2-fluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid



3-{2-[5-Chloro-2-(4-bromo-2-fluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester (60mg, 0.11mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (43mg, 74%).

^{1}H NMR (400MHz, $CDCl_3$) 2.14 (3H, s), 4.89 (2H, s), 6.04 (1H, d, J=2.8Hz), 6.29 (1H, d, J=3.3Hz), 6.49 (1H, s), 6.83-6.93 (3H, m), 7.06-7.11 (2H, m), 7.21 (1H, s), 7.26-7.32 (2H, m's excess).

LC/MS t=3.81 min, [MH+] 531 and 533, [MH-] 529 and 531.

Example 273 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid

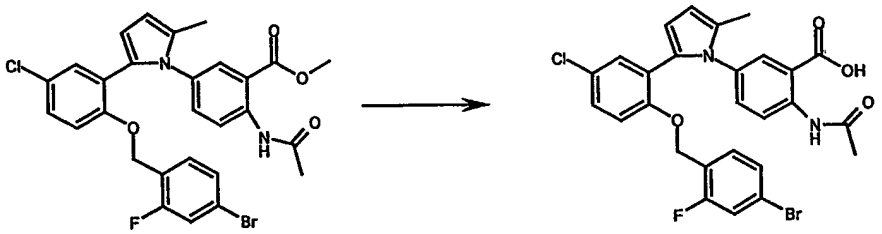
a) 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester

1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.363mmol), 3-amino-6-acetylaminobenzoic acid methyl ester (76mg, 0.363mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4),

filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (129mg, 61%).

^{1}H NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 2.24 (3H, s), 3.81 (3H, s), 4.75 (2H, s), 6.11 (1H, d, J=3.3Hz), 6.26 (1H, d, J=3.5Hz), 6.61 (1H, d, J=8.8Hz), 6.88 (1H, t, J=8.0Hz), 7.08-7.15 (2H, m), 7.19-7.25 (2H, m), 7.26-7.29 (1H, m's excess), 7.67 (1H, d, J=2.5Hz), 8.60 (1H, d, J=9.0Hz), 11.00 (1H, bs).

b) 3-{2-[5-Chloro-2-(4-bromo-2-fluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid



3-{2-[5-Chloro-2-(4-bromo-2-fluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester (129mg, 0.22mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (71.3mg, 57%).

^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 2.26 (3H, s), 4.77 (2H, s), 6.13 (1H, d, J=3.3Hz), 6.27 (1H, d, J=3.3Hz), 6.61 (1H, d, J=8.5Hz), 6.88 (1H, t, J=8.0Hz), 7.10 (1H, dd, J=2.5Hz, J=8Hz), 7.16-7.24 (3H, m), 7.25-7.29 (1H, m's excess), 7.74 (1H, d, J=2.5Hz), 8.63 (1H, d, J=8.8Hz), 10.85 (1H, bs).

LC/MS t=4.31 min, [MH+] 573 and 575, [MH-] 571 and 573.

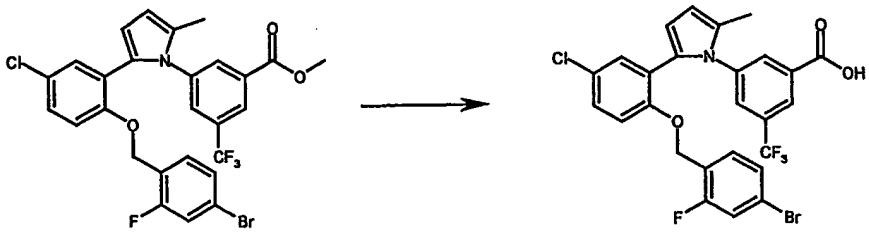
Example 274 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid

a) 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester

1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.363mmol), 3-amino-5-trifluoromethylbenzoic acid methyl ester (80mg, 0.363mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (0-5%) to give the title compound (78mg, 36%).

^{1}H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 3.90 (3H, s), 4.70 (2H, s), 6.16 (1H, d, J=3.0Hz), 6.30 (1H, d, J=3.3Hz), 6.60 (1H, d, J=8.8Hz), 6.85-6.91 (1H, m), 7.10-7.15 (1H, m), 7.21 (1H, s), 7.23 (1H, s), 7.26-7.29 (1H, m's excess), 7.39 (1H, s), 7.84 (1H, s), 8.15 (1H, s).

b) 3-{2-[5-Chloro-2-(4-bromo-2-fluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid



3-{2-[5-Chloro-2-(4-bromo-2-fluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester (78mg, 0.13mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (61mg, 81%).

^{1}H NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 4.71 (2H, s), 6.18 (1H, d, J=3.5Hz), 6.31 (1H, d, J=3.5Hz), 6.62 (1H, d, J=9.0Hz), 6.89 (1H, t, J=8.3Hz), 7.14 (1H, dd, J=2.5Hz, J=8.8Hz), 7.19-7.25 (2H, m), 7.29 (1H, d, J=2.8Hz), 7.45 (1H, s), 7.90 (1H, s), 8.22 (1H, s).

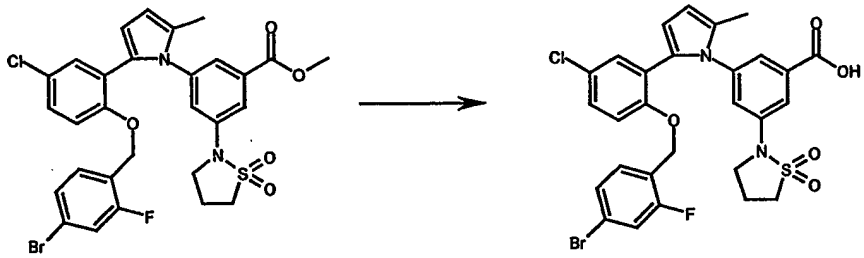
Example 275 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid

a) 3-{2-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid methyl ester

1-[5-Chloro-2-(4-bromo-2-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.363mmol), 3-amino-5--(1,1-dioxo-1*l*^{6}-isothiazolidin-2-yl)-benzoic acid methyl ester (98mg, 0.363mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (30-50%) to give the title compound (152mg, 65%).

^{1}H NMR (400MHz, $CDCl_3$) 2.23 (3H, s), 2.52 (2H, t, J=6.5Hz), 3.30-3.38 (2H, m), 3.52-3.59 (2H, m), 3.86 (3H, s), 4.77 (2H, s), 6.12 (1H, s), 6.27 (1H, s), 6.60 (1H, d, J=8.3Hz), 6.87 (1H, t, J=7.8Hz), 7.06-7.23 (4H, m), 7.24-7.29 (1H, m's excess), 7.45 (1H, s), 7.68 (1H, s).

b) 3-{2-[5-Chloro-2-(4-bromo-2-fluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-isothiazolidin-2-yl)-benzoic acid



3-{2-[5-Chloro-2-(4-bromo-2-fluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid methyl ester (152mg, 0.23mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (74.5mg, 51%).

^{1}H NMR (400MHz, $CDCl_3$) 2.21 (3H, s), 2.46-2.56 (2H, m), 3.32-3.38 (2H, m), 3.58 (2H, t, J=6.5Hz), 4.79 (2H, s), 6.11-6.15 (1H, m), 6.27-6.29 (1H, m), 6.57-6.63 (1H, m), 6.82-6.91 (1H, m), 7.07-7.13 (1H, m), 7.18-7.23 (3H, m), 7.25-7.28 (1H, m's excess), 7.46-7.50 (1H, m), 7.66-7.72 (1H, m).

Example 276 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-hydroxy-benzoic acid

a) 5-Chloro-2-(2,6-difluoro-benzyloxy)-benzaldehyde

5-Chlorosalicylaldehyde (5g, 32.05mmol), 2,6-difluorobenzyl bromide (6.64g, 32.05mmol) and K_2CO_3 (8.86g, 64.1mmol) were heated in DMF (35ml, 1M) at 60°C for 3hrs. Upon cooling to room temperature, Et_2O and H_2O were added. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the title compound (7.9g, 87%).

^{1}H NMR (400MHz, $CDCl_3$) 5.25 (2H, s), 6.93-6.99 (2H, m), 7.14 (1H, d, J=9.0Hz), 7.33-7.41 (1H, m), 7.51 (1H, dd, J=2.8Hz, J=9.0Hz), 7.77 (1H, d, J=2.8Hz), 10.32 (1H, s).

b) 1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione

A mixture of 5-chloro-2-(2,6-difluoro-benzyloxy)-benzaldehyde (7.9g, 28mmol), methyl vinyl ketone (2.45ml, 29.41mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (1.06g, 4.2mmol, 0.15eq) and triethylamine (4.9ml, 35mmol) was heated in EtOH (9.3ml, 3M) at 80°C for 5 hours. Upon cooling, the mixture was diluted with EtOAc and washed with sat. NH_4Cl and sat. $NaHCO_3$, dried (Na_2SO_4) filtered and concentrated. The residue was purified by chromatography, using Biotage®, with cyclohexane containing a gradient of EtOAc (5-15%) to give the title compound (3.01g, 30.5%).

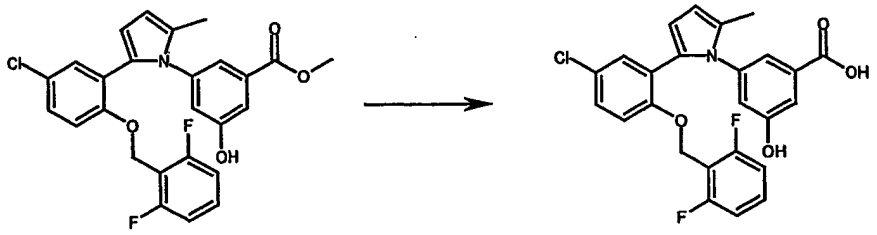
^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 2.72-2.75(2H, m), 3.11-3.15 (2H, m), 5.22 (2H, s), 6.92-6.99 (2H, m's, excess), 7.09 (1H, d, J=9.0Hz), 7.33-7.44 (2H, m's, excess), 7.69 (1H, d, J=2.8Hz).

c) 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-hydroxy-benzoic acid methyl ester

1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-5-hydroxybenzoic acid methyl ester (71mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (68mg, 33%).

^{1}H NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 3.88 (3H, s), 4.87 (2H, s), 6.05 (1H, d, J=3.5Hz), 6.28 (1H, d, J=3.5Hz), 6.62-6.64 (1H, m), 6.83-6.91 (3H, m), 7.06-7.12 (2H, m), 7.28-7.34 (2H, m), 7.40-7.41 (1H, m).

d) 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-hydroxy-benzoic acid

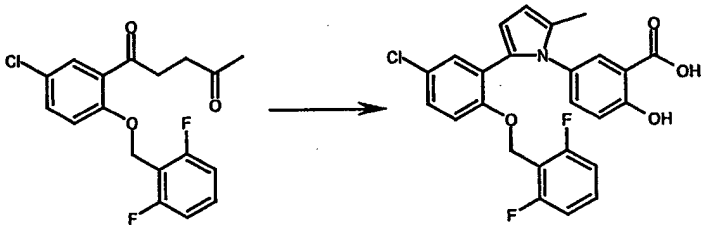


3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-hydroxy-benzoic acid methyl ester (68mg, 0.14mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (37mg, 56%).

^{1}H NMR (400MHz, *d*6 DMSO) 2.02 (3H, s), 4.91 (2H, s), 5.97 (1H, d, J=4.0Hz), 6.16 (1H, d, J=3.5Hz), 6.57 (1H, t, J=2.0Hz), 6.92 (1H, d, J=2.8Hz), 6.95 (1H, t, J=1.5Hz), 7.09-7.14 (3H, m), 7.20-7.25 (2H, m), 7.46-7.53 (1H, m), 9.96 (1H, s).

LC/MS t=3.68 min, [MH+] 470 and 472, [MH-] 468 and 470.

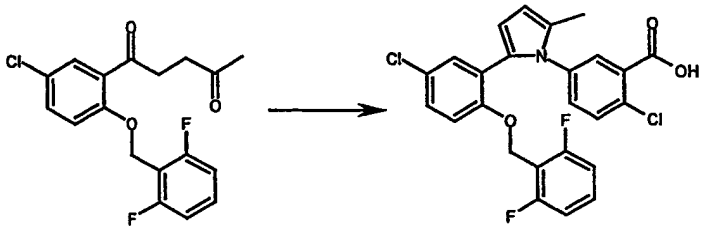
Example 277 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid



1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (200mg, 0.57mmol), 3-amino-6-hydroxybenzoic acid (87mg, 0.57mmol) and pTSA (5mg) were heated in acetonitrile (2.5ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-30%) to give the title compound (95mg, 36%).

^{1}H NMR (400MHz, $CDCl_3$) 2.10 (3H, s), 4.86 (2H, s), 6.04 (1H, d, J=3.3Hz), 6.24 (1H, d, J=3.5Hz), 6.81-6.93 (4H, m), 7.08-7.13 (3H, m), 7.26-7.33 (1H, m's excess), 7.55 (1H, d, J=2.5Hz), 10.52 (1H, bs).

Example 278 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid

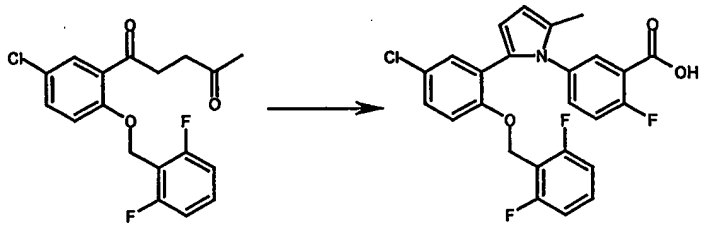


1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-6-chlorobenzoic acid (73.3mg, 0.43mmol) and pTSA (5mg) were heated in

acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (15-30%) to give the title compound (98mg, 48%).

^{1}H NMR (400MHz, $CDCl_3$) 2.14 (3H, s), 4.81 (2H, s), 6.08 (1H, d, J=3.3Hz), 6.23 (1H, d, J=3.3Hz), 6.87 (3H, m), 7.02 (1H, dd, J=2.5Hz, J=8.5Hz), 7.13-7.20 (2H, m), 7.25-7.35 (2H, m's excess), 7.70 (1H, d, J=2.5Hz).

Example 279 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid

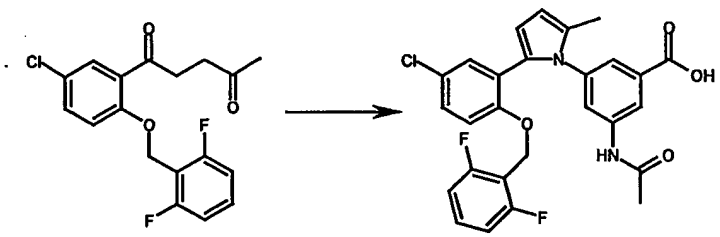


1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-6-fluorobenzoic acid (66mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (46mg, 23%).

^{1}H NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 4.82 (2H, s), 6.07 (1H, s), 6.23 (1H, d, J=2.5Hz), 6.83 (1H, d, J=9.3Hz), 6.90 (2H, t, J=7.8Hz), 7.02 (1H, t, J=9.0Hz), 7.13 (3H, m), 7.31 (1H, m's excess), 7.68 (1H, m).

LC/MS t=3.85 min [MH+] 472, [MH-] 470.

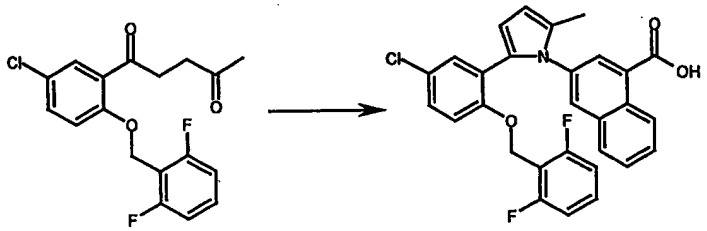
Example 280 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-acetylamino-benzoic acid



1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-5-acetylaminobenzoic acid (83mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (30-50%) to give the title compound (48mg, 22%).

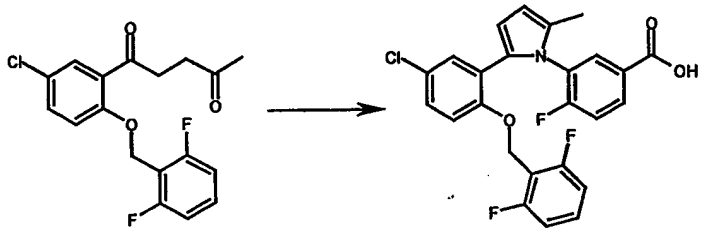
^{1}H NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 2.19 (3H, s), 4.84 (2H, s), 6.06 (1H, s), 6.26 (1H, s), 6.77 (1H, d, J=8.8Hz), 6.86 (2H, t, J=7.8Hz), 7.06 (1H, d, J=8.8Hz), 7.12 (1H, s), 7.43-7.61 (3H, m), 8.05 (1H, s).
LC/MS t=3.53 min [MH+] 511, [MH-] 509

Example 281 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-1-naphthoic acid



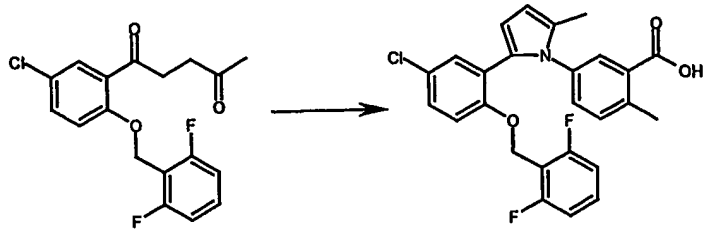
1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-1-naphthoic acid (80mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (66mg, 31%).
^{1}H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 4.79 (2H, s), 6.12 (1H, d, J=3.5Hz), 6.30 (1H, d, J=3.3Hz), 6.75 (1H, d, J=8.8Hz), 6.88 (2H, t, J=7.8Hz), 7.08 (1H, dd, J=2.5Hz, J=8.8Hz), 7.23 (1H, d, J=2.5Hz), 7.24-7.34 (1H, m's excess), 7.54 (1H, t, J=7.3Hz), 7.62-7.69 (2H, m), 7.73 (1H, d, J=8.1Hz), 8.12 (1H, d, J=2.3Hz), 9.07 (1H, d, J=8.6Hz).

Example 282 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-4-fluoro-benzoic acid



1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-4-fluorobenzoic acid (66mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (56mg, 28%).
^{1}H NMR (400MHz, $CDCl_3$) 2.08 (3H, s), 4.85 (2H, s), 6.10 (1H, s), 6.30 (1H, d, J=2.5Hz), 6.78 (1H, d, J=9.0Hz), 6.89 (2H, t, J=7.5Hz), 7.08-7.17 (3H, m), 7.27-7.34 (1H, m's excess), 7.74 (1H, d, J=6.8Hz), 7.99-8.04 (1H, m).

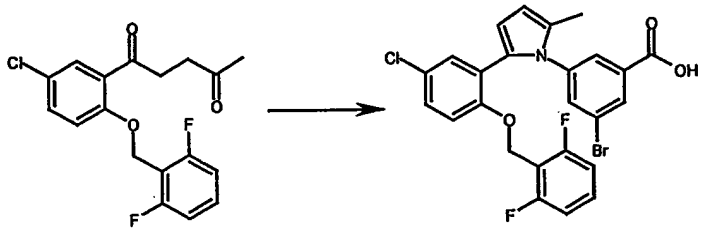
Example 283 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid



1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (131mg, 0.37mmol), 3-amino-6-methylbenzoic acid (56mg, 0.37mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (130mg, 75%).

^{1}H NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 2.63 (3H, s), 4.82 (2H, s), 6.06 (1H, dd, J=0.8Hz, J=3.5Hz), 6.27 (1H, d, J=3.5Hz), 6.80-6.84 (1H, m), 6.86-6.91 (2H, m), 6.96-7.05 (1H, m), 7.08-7.15 (3H, m), 7.26-7.33 (1H, m's excess), 7.75 (1H, d, J=2.3Hz).

Example 284 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-bromo-benzoic acid



1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (131mg, 0.37mmol), 3-amino-5-bromobenzoic acid (80mg, 0.37mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (21mg, 11%).

^{1}H NMR (400MHz, MeOD) 2.07 (3H, s), 4.81 (2H, s), 6.00 (1H, d, J=2.8Hz), 6.12 (1H, d, J=3.5Hz), 6.89-6.99 (3H, m), 7.12-7.21 (2H, m), 7.23 (1H, s), 7.32-7.42 (1H, m), 7.52 (1H, s), 7.97 (1H, s).

Example 285 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid

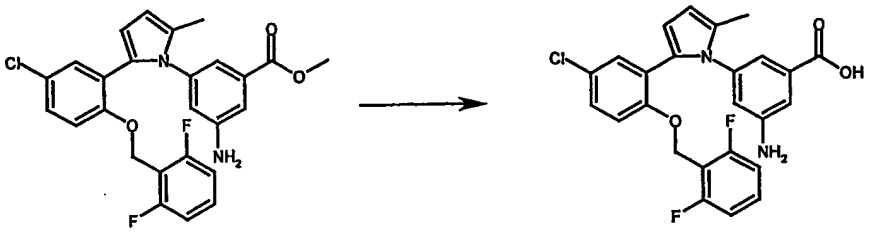
a) 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester

1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3,5-diaminobenzoic acid methyl ester (71mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was

diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (97mg, 48%).

^{1}H NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 3.72 (2H, bs), 3.87 (3H, s), 4.90 (2H, s), 6.03 (1H, d, J=2.8Hz), 6.30 (1H, d, J=3.5Hz), 6.45 (1H, s), 6.83-6.95 (3H, m), 7.01-7.11 (2H, m), 7.16 (1H, s), 7.21-7.31 (2H, m's excess).

b) 3-{2-[5-Chloro-2-(2,6-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid



3-{2-[5-Chloro-2-(2,6-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester (97mg, 0.2mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (72mg, 77%).

^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.80 (2H, s), 6.11 (1H, s), 6.28 (1H, s), 6.47-6.55 (1H, m), 6.62 (1H, d, J=7.8Hz), 6.91-6.99 (1H, m), 7.03-7.11 (1H, m), 7.17-7.34 (5H, m's excess).

LC/MS t=3.55 min, [MH+] 469 and 471, [MH-] 467 and 469.

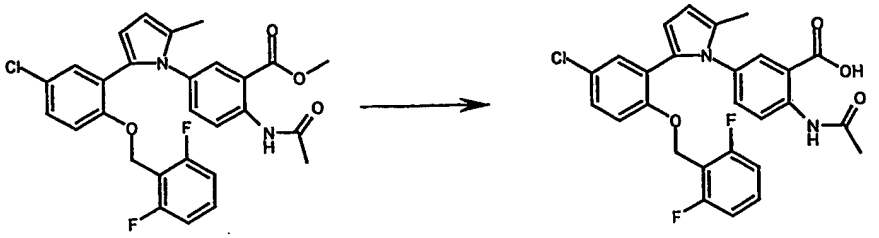
<u>Example 286 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid</u>

a) 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester

1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-6-acetylaminobenzoic acid methyl ester (89mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (102mg, 45%).

^{1}H NMR (400MHz, $CDCl_3$) 2.10 (3H, s), 2.24 (3H, s), 3.86 (3H, s), 4.83 (2H, s), 6.05 (1H, d, J=2.5Hz), 6.24 (1H, d, J=3.5Hz), 6.81 (1H, d, J=8.8Hz), 6.86-6.92 (2H, m), 7.08-7.16 (3H, m), 7.28-7.34 (1H, m), 7.68 (1H, d, J=2.8Hz), 8.61 (1H, d, J=9.0Hz), 11.03 (1H, bs).

b) 3-{2-[5-Chloro-2-(2,6-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid



3-{2-[5-Chloro-2-(2,6-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester (102mg, 0.195mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (78mg, 78%).

^{1}H NMR (400MHz, $CDCl_3$) 2.11 (3H, s), 2.25 (3H, s), 4.83 (2H, s), 6.05 (1H, d, J=4.3Hz), 6.24 (1H, d, J=3.5Hz), 6.82 (1H, d, J=8.5Hz), 6.86-6.93 (2H, m), 7.06-7.20 (3H, m), 7.27-7.34 (1H, m), 7.74 (1H, d, J=2.8Hz), 8.63 (1H, d, J=8.8Hz), 10.88 (1H, bs).

LC/MS t=3.97 min, [MH+] 511 and 513, [MH-] 509 and 511.

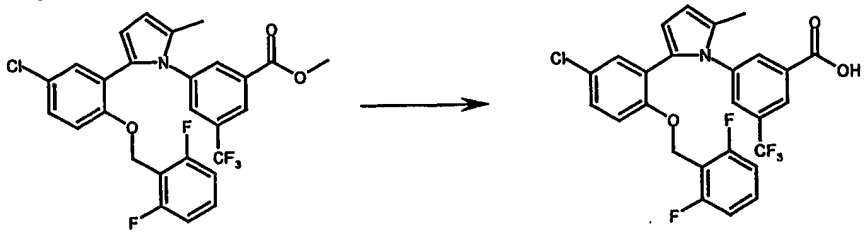
Example 287 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid

a) 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester

1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-5-trifluoromethylbenzoic acid methyl ester (93mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (0-5%) to give the title compound (73mg, 32%).

^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 3.93 (3H, s), 4.78 (2H, s), 6.09 (1H, d, J=3.5Hz), 6.25 (1H, d, J=3.5Hz), 6.81 (1H, d, J=8.5Hz), 6.83-6.91 (2H, m), 7.12-7.18 (2H, m), 7.26-7.34 (1H, m's excess), 7.39 (1H, s), 7.86 (1H, s), 8.15 (1H, s).

b) 3-{2-[5-Chloro-2-(2,6-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid



3-{2-[5-Chloro-2-(2,6-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester (73mg, 0.136mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (55mg, 78%).

^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.77 (2H, s), 6.11 (1H, d, J=4.0Hz), 6.25 (1H, d, J=3.5Hz), 6.81 (1H, d, J=8.8Hz), 6.84-6.90 (2H, m), 7.14-7.18 (1H, m), 7.21 (1H, d, J=2.5Hz), 7.26-7.31 (1H, m's excess), 7.44 (1H, s), 7.90 (1H, s), 8.21 (1H, s).

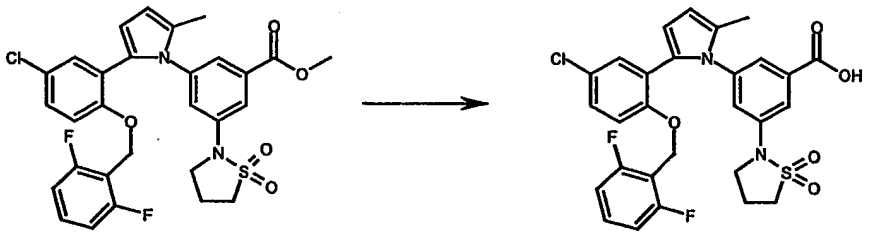
Example 288 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid

a) 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid methyl ester

1-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-5-(1,1-dioxo-1*l*^{6}-*iso*thiazolidin-2-yl)-benzoic acid methyl ester (115mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (30-50%) to give the title compound (106mg, 42%).

^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 2.47-2.56 (2H, m), 3.36 (2H, t, J=7.5Hz), 3.59 (2H, t, J=6.5Hz), 3.89 (3H, s), 4.84 (2H, s), 6.05 (1H, d, J=3.3Hz), 6.25 (1H, d, J=3.5Hz), 6.80-6.89 (3H, m), 7.07-7.13 (3H, m), 7.25-7.32 (1H, m's excess), 7.49 (1H, t, J=1.5Hz), 7.74-7.76 (1H, m).

b) 3-{2-[5-Chloro-2-(2,6-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-isothiazolidin-2-yl)-benzoic acid



3-{2-[5-Chloro-2-(2,6-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-isothiazolidin-2-yl)-benzoic acid methyl ester (106mg, 0.18mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (71mg, 69%).

^{1}H NMR (400MHz, $CDCl_3$) 2.19 (3H, s), 2.48-2.57 (2H, m), 3.34-3.40 (2H, m), 3.60 (2H, t, J=6.5Hz), 4.83 (2H, s), 6.07 (1H, d, J=4.3Hz), 6.25 (1H, d, J=3.5Hz), 6.81-6.90 (3H, m), 7.11-7.17 (3H, m), 7.25-7.32 (1H, m's excess), 7.52 (1H, t, J=1.5Hz), 7.79 (1H, t, J=1.5Hz).

Example 289 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-hydroxy-benzoic acid

a) 5-Chloro-2-(2,3-difluoro-benzyloxy)-benzaldehyde

5-Chlorosalicylaldehyde (10g, 63.7mmol), 2,3-difluorobenzyl bromide (8.08ml, 63.7mmol) and K_2CO_3 (17.6g, 127.4mmol) were heated in DMF (64ml, 1M) at 60°C for 3hrs. Upon cooling to room temperature, Et_2O and H_2O were added. The layers were separated and

the aqueous phase was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the title compound (13.4g, 74.3%).
^1H NMR (400MHz, $CDCl_3$) 5.27 (2H, s), 7.04 (1H, d, J=8.8Hz), 7.20 (3H, m's excess), 7.50 (1H, dd, J=2.8Hz, J=9.0Hz), 7.81 (1H, d, J=2.8Hz), 10.44 (1H, s).

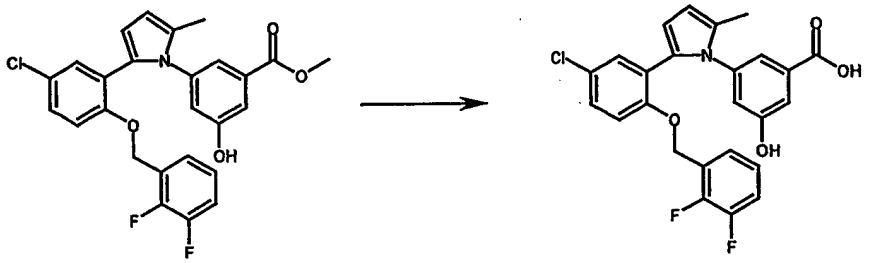
b) 1-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione

A mixture of 5-chloro-2-(2,3-difluoro-benzyloxy)-benzaldehyde (13.4g, 47.3mmol), methyl vinyl ketone (3.36ml, 56.8mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (1.7g, 7.1mmol, 0.15eq) and triethylamine (6.07ml, 82.8mmol) was heated in EtOH (16ml, 3M) at 80°C for 18 hours. Upon cooling, the mixture was diluted with EtOAc and washed with sat. NH_4Cl and sat. $NaHCO_3$, dried (Na_2SO_4) filtered and concentrated. The residue was purified by chromatography, using Biotage®, with cyclohexane containing a gradient of EtOAc (10-15%) to give the title compound (4.16g, 25%).
^1H NMR (400MHz, $CDCl_3$) 2.21 (3H, s), 2.81 (2H, t, J=6.3Hz), 3.21 (2H, t, J=6.3Hz), 5.24 (2H, s), 6.99 (1H, d, J=9.0Hz), 7.10-7.31 (3H, m's excess), 7.41 (1H, dd, J=2.8Hz, J=8.8Hz), 7.71 (1H, d, J=2.8Hz).

c) 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-hydroxy-benzoic acid methyl ester

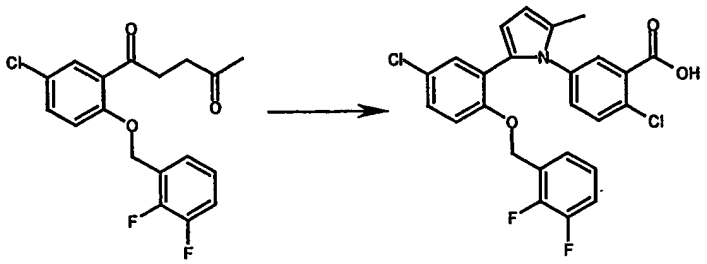
1-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.42mmol), 3-amino-5-hydroxybenzoic acid methyl ester (71mg, 0.42mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (91mg, 45%).
^1H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 3.84 (3H, s), 4.84 (2H, s), 5.19 (1H, s), 6.12 (1H, d, J=2.8Hz), 6.29 (1H, d, J=3.5Hz), 6.61-6.67 (2H, m), 6.80-6.87 (1H, m), 6.97-7.04 (1H, m), 7.05-7.13 (1H, m), 7.20-7.24 (1H, m), 7.30 (1H, t, J=1.5Hz), 7.41 (1H, m).

d) 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-hydroxy-benzoic acid



3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-hydroxy-benzoic acid methyl ester (91mg, 0.19mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (78mg, 87%).
^1H NMR (400MHz, MeOD) 2.11 (3H, s), 4.86 (2H, m's excess), 6.19 (1H, s), 6.57 (1H, t, J=2.3Hz), 6.81 (1H, d, J=8.8Hz), 6.85-6.91(1H, m), 7.02-7.21 (6H, m), 7.30 (1H, s).
LC/MS t=3.74 min [MH+] 470, [MH-] 468

Example 290 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid

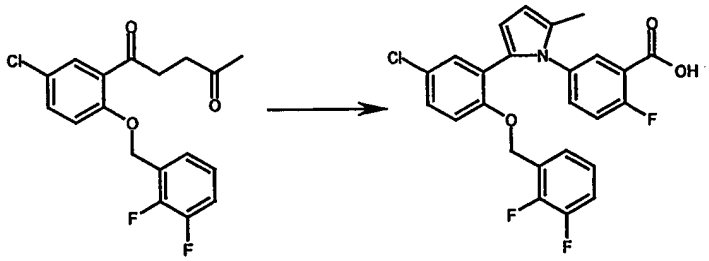


1-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-6-chlorobenzoic acid (73.3mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (109mg, 53%).

^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.84 (2H, s), 6.14 (1H, d, J=3.3Hz), 6.28 (1H, d, J=3.3Hz), 6.61-6.72 (2H, m), 6.97-7.16 (5H, m), 7.28-7.36 (1H, m's excess), 7.69 (1H, d, J=2.5Hz).

LC/MS t=4.10 min [MH+] 489.

Example 291 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid

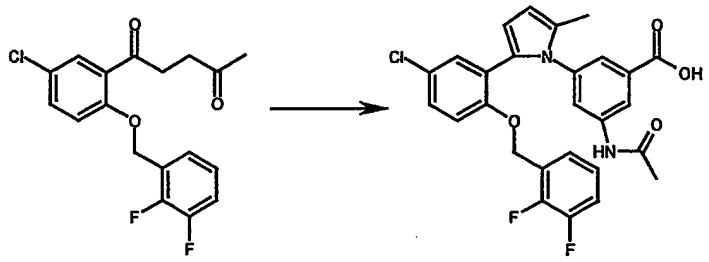


1-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-6-fluorobenzoic acid (66mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (61mg, 31%).

^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.86 (2H, s), 6.15 (1H, d, J=3.3Hz), 6.29 (1H, d, J=3.5Hz), 6.65 (1H, d, J=8.8Hz), 6.78 (1H, t, J=6.0Hz), 6.98-7.19 (6H, m), 7.71 (1H, dd, J=2.8Hz, J=6.3Hz).

LC/MS t=3.92 min [MH+] 472, [MH-] 470.

Example 292 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-acetylamino-benzoic acid

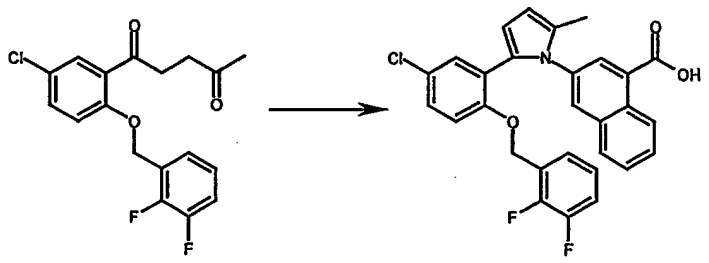


1-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-5-acetylaminobenzoic acid (83mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (30-50%) to give the title compound (44mg, 21%).

^{1}H NMR (400MHz, MeOD) 2.05 (3H, s), 2.11 (3H, s), 4.84 (2H, s), 6.03 (1H, d, J=3.0Hz), 6.20 (1H, d, J=3.5Hz), 6.73 (1H, d, J=8.8Hz), 6.85 (1H, t, J=7.3Hz), 7.00-7.09 (2H, m), 7.10-7.21 (2H, m), 7.35 (1H, s), 7.50 (1H, s), 7.98 (1H, s).

LC/MS t=3.60 min [MH+] 511

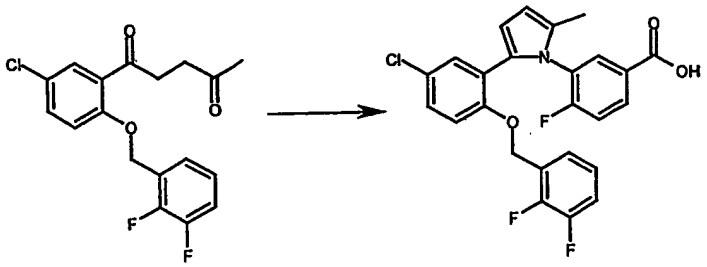
Example 293 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-1-naphthoic acid



1-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-1-naphthoic acid (80mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-15%) to give the title compound (59mg, 28%).

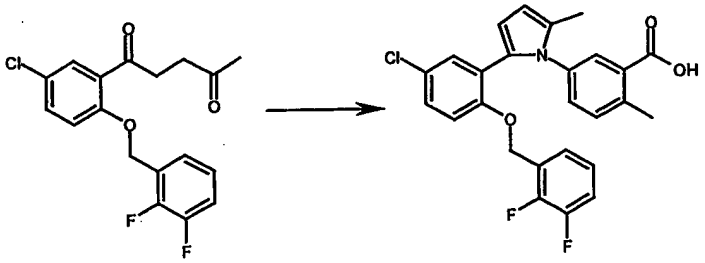
^{1}H NMR (400MHz, $CDCl_3$) 2.22 (3H, s), 4.77 (2H, s), 6.20 (1H, d, J=2.8Hz), 6.34 (1H, d, J=3.5Hz), 6.47-6.60 (2H, m), 6.80 (1H, q, J=8.1Hz), 6.97-7.09 (2H, m), 7.39 (1H, d, J=2.8Hz), 7.54 (1H, t, J=7.3Hz), 7.61-7.71 (3H, m), 8.13 (1H, s), 9.05 (1H, d, J=9.1Hz).

Example 294 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-4-fluoro-benzoic acid



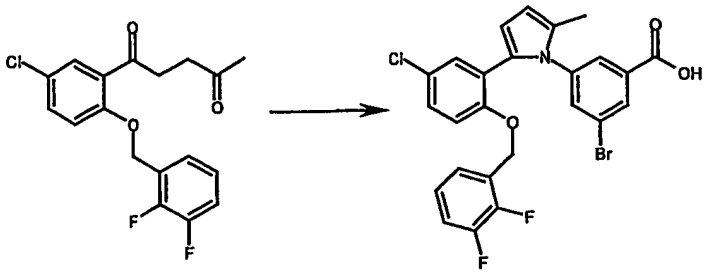
1-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-4-fluorobenzoic acid (66mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-15%) to give the title compound (48mg, 24%).
^{1}H NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 4.90 (2H, s), 6.17 (1H, d, J=2.8Hz), 6.33 (1H, d, J=3.3Hz), 6.62 (1H, d, J=8.8Hz), 6.82 (1H, t, J=6.3Hz), 6.94-7.20 (4H, m), 7.24 (1H, d, J=2.5Hz), 7.80 (1H, dd, J=2.3Hz, J=7.1Hz), 8.01-8.07 (1H, m).

Example 295 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid



1-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-6-methylbenzoic acid (64.3mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-15%) to give the title compound (116mg, 58%).
^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 2.64 (3H, s), 4.84 (2H, s), 6.14 (1H, d, J=3.3Hz), 6.30 (1H, d, J=3.3Hz), 6.62 (1H, d, J=8.8Hz), 6.74-6.80 (1H, m), 6.95-7.16 (6H, m), 7.78 (1H, d, J=2.0Hz).

Example 296 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-bromo-benzoic acid



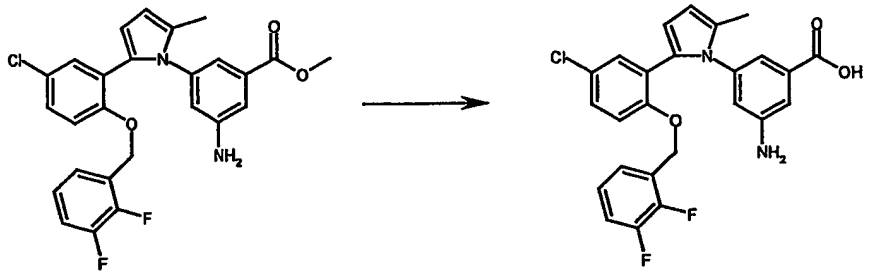
1-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-5-bromobenzoic acid (92mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-20%) to give the title compound (48mg, 21%).
^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.82 (2H, s), 6.14 (1H, d, J=2.5Hz), 6.30 (1H, d, J=3.5Hz), 6.66 (1H, d, J=8.8Hz), 6.75-6.82 (1H, m), 6.98-7.18 (4H, m), 7.34 (1H, s), 7.65 (1H, s), 8.10 (1H, s).

Example 297 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid

a) 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester

1-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3,5-diaminobenzoic acid methyl ester (71mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-15%) to give the title compound (102mg, 50%).
^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 3.82 (3H, s), 4.86 (2H, s), 6.10 (1H, d, J=2.8Hz), 6.30 (1H, d, J=3.3Hz), 6.64 (1H, d, J=8.9Hz), 6.85 (1H, t, J=6.3Hz), 6.97-7.05 (1H, m), 7.06-7.14 (3H, m), 7.19-7.24 (2H, m).

b) 3-{2-[5-Chloro-2-(2,3-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid



3-{2-[5-Chloro-2-(2,3-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester (102mg, 0.21mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was

diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (70mg, 71%).
^{1}H NMR (400MHz, MeOD) 2.13 (3H, s), 4.84 (2H, s), 6.11 (1H, d, J=2.8Hz), 6.23 (1H, d, J=3.5Hz), 6.81-6.91 (2H, m), 7.03-7.12 (1H, m), 7.13-7.27 (4H, m), 7.66 (1H, s), 7.85 (1H, s).
LC/MS t=3.63 min [MH+] 469, [MH-] 467

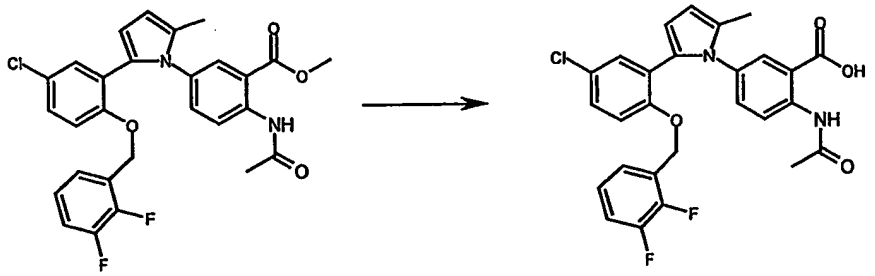
Example 298 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid

a) 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester

1-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-6-acetylaminobenzoic acid methyl ester (89mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (10-15%) to give the title compound (110mg, 50%).
^{1}H NMR (400MHz, MeOD) 2.09 (3H, s), 2.19 (3H, s), 3.79 (3H, s), 4.83 (2H, s), 6.06 (1H, d, J=3.5Hz), 6.18 (1H, d, J=3.5Hz), 6.81 (1H, d, J=8.8Hz), 6.85-6.91 (1H, m), 7.03-7.27 (5H, m), 7.58 (1H, d, J=2.5Hz), 8.34 (1H, d, J=8.8Hz).

b) 3-{2-[5-Chloro-2-(2,3-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid

3-{2-[5-Chloro-2-(2,3-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-



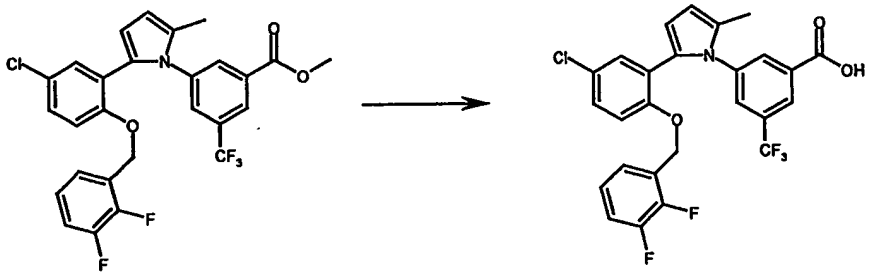
benzoic acid methyl ester (110mg, 0.21mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (86mg, 80%).
^{1}H NMR (400MHz, MeOD) 2.08 (3H, s), 2.17 (3H, s), 4.83 (2H, s), 6.80 (1H, d, J=8.8Hz), 6.82-6.89 (1H, m), 7.00-7.25 (7H, m), 7.64 (1H, d, J=2.8Hz), 8.41 (1H, d, J=9.0Hz).
LC/MS t=511 min [MH+] 511, [MH-] 509.

Example 299 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid

a) 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester

1-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-5-trifluoromethylbenzoic acid methyl ester (93mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (0-5%) to give the title compound (107mg, 48%).
^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 3.90 (3H, s), 4.77 (2H, s), 6.16 (1H, d, J=3.0Hz), 6.31 (1H, d, J=3.5Hz), 6.62 (1H, d, J=8.8Hz), 6.71-6.77 (1H, m), 6.96-7.03 (1H, m), 7.06-7.16 (2H, m), 7.25-7.31 (1H, m's excess), 7.39 (1H, s), 7.84 (1H, s), 8.15 (1H, s).

b) 3-{2-[5-Chloro-2-(2,3-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid



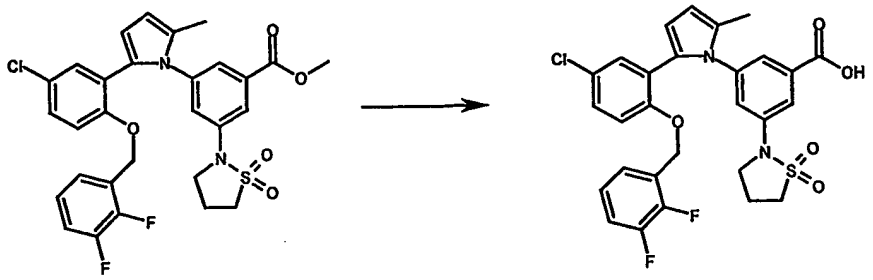
3-{2-[5-Chloro-2-(2,3-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester (107mg, 0.20mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (73mg, 70%).
^{1}H NMR (400MHz, MeOD) 2.14 (3H, s), 4.76 (2H, s), 6.12 (1H, d, J=2.8Hz), 6.23 (1H, d, J=3.5Hz), 6.77-6.86 (2H, m), 7.02-7.11 (1H, m), 7.14-7.23 (2H, m), 7.29 (1H, d, J=2.8Hz), 7.37 (1H, s), 7.78 (1H, s), 8.09 (1H, s).

Example 300 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*isothiazolidin*-2-yl)-benzoic acid

a) 3-{2-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1*l*^{6}-*isothiazolidin*-2-yl)-benzoic acid methyl ester

1-[5-Chloro-2-(2,3-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (150mg, 0.43mmol), 3-amino-5-(1,1-dioxo-1*l*^{6}-*isothiazolidin*-2-yl)-benzoic acid methyl ester (115mg, 0.43mmol) and pTSA (5mg) were heated in acetonitrile (2ml) at 160°C for 10 minutes in the microwave. Upon cooling, the mixture was diluted with DCM and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, on silica, with cyclohexane containing a gradient of EtOAc (20-30%) to give the title compound (152mg, 62%).
^{1}H NMR (400MHz, MeOD) 2.14 (3H, s), 2.44 (2H, quin, J=6.8Hz), 3.39 (2H, t, J=7.3Hz), 3.55 (2H, t, J=6.5Hz), 3.82 (3H, s), 4.81 (2H, s), 6.08 (1H, d, J=3.3Hz), 6.20 (1H, d, J=3.5Hz), 6.76-6.85 (2H, m), 7.02-7.10 (2H, m), 7.12-7.20 (2H, m), 7.24 (1H, d, J=2.5Hz), 7.29 (1H, t, J=1.5Hz), 7.71 (1H, m).

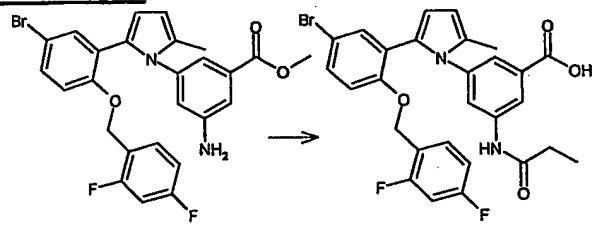
b) 3-{2-[5-Chloro-2-(2,3-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*isothiazolidin*-2-yl)-benzoic acid



3-{2-[5-Chloro-2-(2,3-difluoro -benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*isothiazolidin*-2-yl)-benzoic acid methyl ester (152mg, 0.26mmol) was heated in a mixture of EtOH (4ml) and 2M NaOH (0.5ml) at 120°C for 5 minutes in the microwave. Upon cooling, the mixture was diluted with DCM, washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (120mg, 95%).

^{1}H NMR (400MHz, MeOD) 2.14 (3H, s), 2.44 (2H, quin, J=7.0Hz), 3.38 (2H, t, J=7.3Hz), 3.52-3.64 (2H, m's excess), 4.83 (2H, s), 6.19 (1H, s), 6.75-6.91 (2H, m), 6.99-7.28 (6H, m), 7.32 (1H, t, J=1.5Hz), 7.72 (1H, m).

Example 301: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-propionylamino-benzoic acid

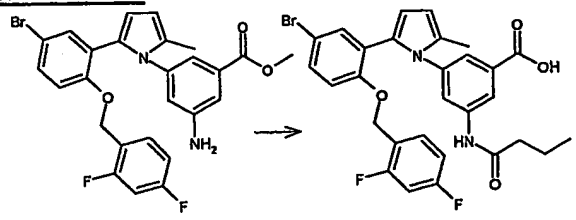


5-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester (264mg, 0.5mmol) was dissolved DCM (2mL) containing pyridine (0.1mL) and DMAP (60mg, cat). Propionyl chloride (70µL) was added dropwise.The reaction mixture was stirred overnight at room temperature, then diluted with DCM (15mL) and washed sequentially with 2M HCl and water, dried ($MgSO_4$), filtered and evaporated. The residue was purified on a Water's sep-pack (10.0g) with Et_2O/iso-hexane to give, after evaporation, the intermediate ester. The ester was then heated at 60°C for 1 hour in MeOH (3mL) and 2M NaOH (2mL). Upon cooling the solvent volume was reduced to approximately 1mL then neutralised with 2M HCl (2mL), diluted with water (10mL) and extracted with DCM (10mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated to give the title compound (80mg, 30%).

^{1}H NMR (400MHz, $CDCl_3$) 1.22 (3H, t ,J=7Hz), 2.17 (3H, s), 2.33-2.42 (2H, m), 4.78 (2H, s), 6.11 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.56 (1H, d J=9Hz), 6.72-6.83 (2H, m), 6.99-7.07 (1H, m), 7.17-7.22 (2H, m), 7.35 (1H, d, J=2Hz), 7.45 (1H, s), 7.62 (1H, s), 7.98 (1H, s).

LC/MS t=3.88 min [MH^+] 571

Example 302: 3-{2-{5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-butyrylamino-benzoic acid

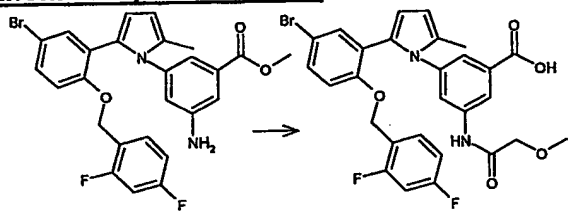


Prepared in the same way as 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-propionylamino-benzoic acid using the appropriate acid chloride, to give the title compound (80mg, 28%).

^{1}H NMR (400MHz, $CDCl_3$) 0.98 (3H, t, J=7Hz), 1.67-1.78 (2H, m), 2.16 (3H, s), 2.26-2.34 (2H, m), 4.78 (2H, s), 6.11 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.56 (1H, d, J=9Hz), 6.72-6.83 (2H, m), 6.96-7.06 (1H, m), 7.17-7.23 (2H, m), 7.36 (1H, d, J=2Hz), 7.46 (1H, s), 7.61 (1H, s), 7.98 (1H, s)

LC/MS t=3.98 min [MH^+] 585.

Example 303: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-methoxy-ethanolamino)-benzoic acid

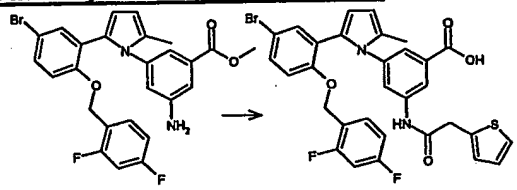


Prepared in the same way as 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-propionylamino-benzoic acid using the appropriate acid chloride, to give the title compund (60mg, 20%).

^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 3.50 (3H, s), 3.99 (2H, s), 4.79 (2H, s), 6.11 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.57 (1H, d, J=9Hz), 6.73-6.84 (2H, m), 6.98 7.08 (1H, m), 7.22 (1H, d, J=2Hz), 7.37 (1H, d, J=2Hz), 7.47 (1H, t, J=1.5Hz), 7.73 (1H, t, J=1.5Hz), 7.99 (1H, t, J=1.5Hz), 8.26 (1H,s).

LC/MS t=3.81 min [MH^+] 587

Example 304: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl]}-5-(2-thiophen-2-yl-ethanoylamino)-benzoic acid

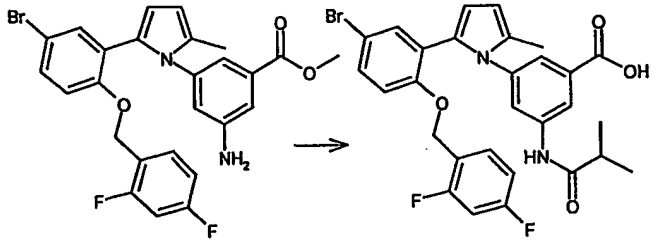


Prepared in the same way as 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-propionylamino-benzoic acid using the appropriate acid chloride, to give the title compound (120mg, 38%).

^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 3.92 (2H, s), 4.77 (2H, s), 6.10 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.55 (1H, d, J=8Hz), 6.72-6.82 (2H, m), 6.96-7.18 (3H,m),7.17-7.24 (1H, m), 7.29-7.36 (3H, m), 7.46 (1H, t, J=1.5Hz), 7.60 (1H, t, J=1.5Hz), 7.83 (1H, t, J=1.5Hz).

LC/MS t=4.06 min [MH^+] 639

Example 305: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-methyl-propanoylamino)-benzoic acid

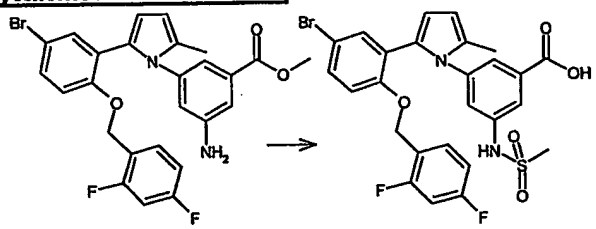


Prepared in the same way as 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-propionylamino-benzoic acid using the appropriate acid chloride, to give the title compound (170mg, 58%).

^{1}H NMR (400MHz, $CDCl_3$) 1.23 (6H, d, J=7Hz), 2.17 (3H, s), 2.43-2.52 (1H, m), 4.79 (2H, s), 6.10 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.57 (1H, d, J=9Hz), 6.72-6.83 (2H, m), 6.98 (1H, m), 7.17 (2H, m), 7.36 (1H, d, J=3Hz), 7.40 (1H, br s), 7.56 (1H, br s), 7.99 (1H, br s).

LC/MS t=3.99 min [MH^+] 585.

Example 306: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-methanesulfonylamino-benzoic acid

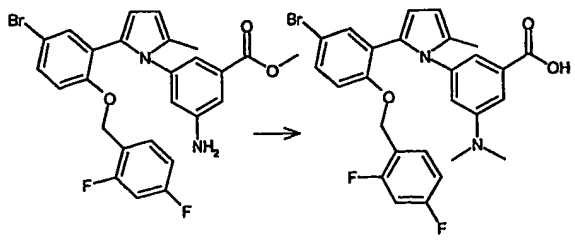


Prepared in the same way as 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-propionylamino-benzoic acid, to give the title compound (150mg, 58%).

^{1}H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 2.72 (3H, s), 4.78 (2H, s), 6.13 (1H, d, J=3Hz) 6.30 (1H, d, J=3Hz), 6.62 (1H, d, J=8Hz), 6.74-6.85 (2H, m), 7.00-7.10 (2H, m), 7.17-7.24 (2H, m), 7.34 (1H, s), 7.57 (1H, s), 7.73 (1H, s).

LC/MS t=3.81 min [MH^+] 593.

Example 307: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-dimethylamino-benzoic acid

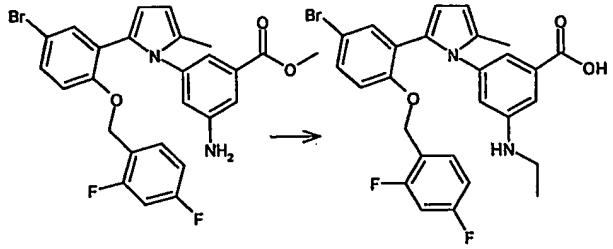


3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester (236mg, 0.5mmol) in DMF (2.5mL), was treated with sodium hydride (60% suspension) (100mg, 2.5mmol) under nitrogen. The reaction mixture was stirred for 30 minutes at room temperature before adding iodomethane (0.2ml,1.3mmol). The mixture was stirred at room temperature for a further 2 hours, then quenched with water (2mL) and stirred over night. The mixture was then further diluted with water (10mL) and the pH was adjusted to pH~6 with glacial acetic acid, extacted with DCM, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on a Water's sep-pack (10g) with Et_2O/iso-hexane to give the title compound (70mg,25%).

^1H NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 2.80 (6H, s), 4.77 (2H, s), 6.12 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.45 (1H, t, J=2Hz), 6.56 (1H, d, J=9Hz), 6.72-6.82 (2H, m), 6.94-7.03 (1H, m), 7.15 (1H, s), 7.18-7.24 (1H, m), 7.28 (1H, s), 7.38 (1H, d, J=2Hz)

LC/MS t=4.10 mins [MH^+] 543.

Example 308: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-ethylamino -benzoic acid

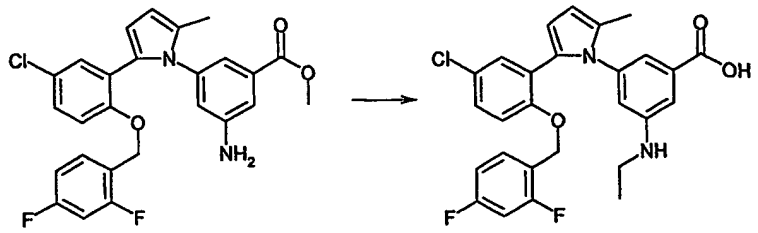


Prepared in the same way as 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-dimethylamino-benzoic acid, using 2.6 equivalent of ethyl iodide (60mg, 22%).

^1H NMR (400MHz, $CDCl_3$) 1.23 (3H, t, J=7Hz), 2.18 (3H, s), 2.98 (2H, q, J=7Hz), 4.80 (2H, s), 6.10 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.36 (1H, t, J=1.5Hz), 6.58 (1H, d, J=9Hz), 6.73-6.83 (2H, m), 6.99-7.06 (2H, m), 7.10 (1H, t, J=1.5Hz), 7.17 (1H, t, J=1.5Hz), 7.18-7.23 (1H, dd, J=3Hz, J=7Hz), 7.36 (1H, d, J=3Hz).

LC/MS t=4.02 min [MH^+] 543.

Eaxmple 309: 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-ethylamino-benzoic acid

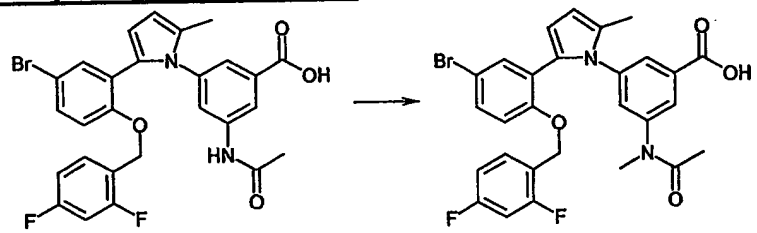


Prepared in the same way as 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-dimethylamino-benzoic acid, using 2.6 equivalents of ethyl iodide (52mg, 21%).

^{1}H NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=6Hz), 2.16 (3H, s), 4.27 (2H, q, J=7Hz), 4.81 (2H, s), 6.09 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.43 (1H, t, J=2Hz), 6.63 (1H, d, J=9Hz), 6.75-6.84 (2H, m), 6.98-7.10 (2H, m), 7.13 (1H, t, J=1.5Hz), 7.19 (1H, d, J=3Hz), 7.23 (1H, t, J=1.5Hz).

LC/MS t=4.07 min [MH^+] 497.

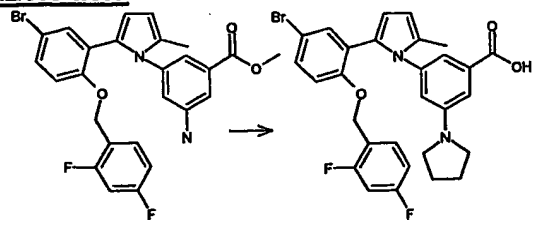
Example 310: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)phenyl]-5-methyl-pyrrol-1-yll}-5-(acetyl-methyl amino)-benzoic acid



3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-acetylamino)-benzoic acid (200mg, 0.36mmol)was dissolved in DMF (2.5ml). Sodium hydride (60% suspension) (40mg, 0.72mmol) was added, followed by iodomethane (0.06mL, 0.8mmol). The reaction mixture was stirred at room temperature under nitrogen for 4 hours, then water (2mL) was added and stirring continued overnight. The mixture was further diluted with water (10mL) and extracted with EtOAc, dried ($MgSO_4$), filtered and evaporated. The residue was chromatographed on a water's sep-pack (10g) with Et_2O/iso-hexane to give the title compound (48mg, 23%).

LC/MS t=3.71 min [MH^+] 571

Example 311: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-pyrrolidin-1-yl-benzoic acid

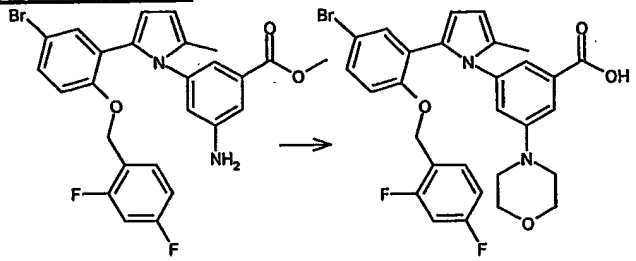


3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}5-amino-benzoic acid methyl ester, (187mg, 0.35mmol) was dissolved in 2-butanone (2.5mL). Potassium cabonate (0.700g)and 1,4-dibromobutane (0.2mL, 1.5mmol) were added. The mixture was heated at reflux under nitrogen for 72 hrs, cooled, filtered through celite and evaporated. The residue was purified on a Water's sep-pack (10g) with Et_2O/iso-hexane to give the intermediate ester (140mg, 68%). The free acid was obtained by heating the ester (128mg, 0.2mmol) in MeOH (3mL) and 2M NaOH (2mL) at 60°C for 1 hour. Upon cooling, the MeOH was evaporated and the residue was then neutralised with 2M HCl (2mL) and extracted with EtOAc (10mL). The organic phase was dried ($MgSO_4$), filtered and evaporated to give the title comppound (115mg, 62%).

^{1}H NMR (400MHz, $CDCl_3$) 1.91-1.98 (4H, m), 2.19 (3H, s), 3.05-3.13 (4H, m), 4.80 (2H, s), 6.11 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.31 (1H, t, J=2Hz), 6.56 (1H, d, J=9Hz), 6.73-6.81 (2H, m), 6.96-7.03 (1H, m), 7.08 (1H, t, J=1.5Hz), 7.12 (1H, t, J=1.5Hz), 7.18-7.22 (1H, dd, J=2Hz), 7.38 (1H, d, J=2Hz)

LC/MS t=4.25 mins [MH^+] 569

Example 312: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-morpholin-1-yl-benzoic acid



This compound was synthesised in the same way as 3-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-pyrrolidin-1-yl-benzoic acid using the appropriate chloride to give the title compound (110mg, 38%).

^{1}H NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 2.93 (4H, t, J=4Hz), 3.76 (4H, t, J=4Hz), 4.75 (2H, s), 6.11 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.57 (1H, d, J=9Hz), 6.63 (1H, t, J=2Hz), 6.73-6.83 (2H, m), 6.95-7.03 (1H, m), 7.23 (1H, dd, J=2Hz, J=6Hz), 7.28 (1H, t, J=1.5Hz), 7.38 (1H, d, J=3Hz), 7.46 (1H, t, J=1.5Hz).

LC/MS t=2.96 min [MH^+] 585

Example 313: -3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid

a) 3-amino-6-hydroxy-benzoic-acid-methyl ester

Methyl-2-hydroxy-5-nitrobenzoate (1.000, 5.0mmol) was stirred under a hydrogen atmosphere at room temperature in methanol (20ml) with palladium on charcoal for 3 hours. The reaction mixture was filtered through celite and evaporated to give the title compound, which was used without further purification.

LC/MS t=1.54 min [MH^+] 168

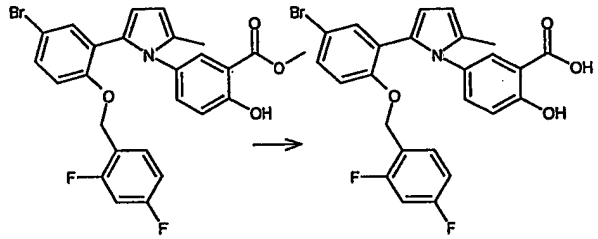
b) 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid methyl ester

1-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]-pentane-1,4-dione (600mg, 1.5mmol), methyl-3-amino-6-hydroxy-benzoate (800mg, ~33%pure, 1.5mmol), pTSA (cat), and powdered 4A molecular sieves (1.0g) were heated at reflux in in toluene (10ml) for 18 hours, cooled, filtered through celite and evaporated. The residue was purified by chromatography on silica gel with Et_2O/iso-hexane, as eluant, to give the title compound (657mg, 82%).

^1H NMR (400MHz, $CDCl_3$) 2.11 (3H, s), 3.84 (3H, s), 4.79 (2H, s), 6.09 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.58 (1H, d, J=9Hz), 6.76-6.85 (3H, m), 6.97-7.07 (2H, m), 7.21-7.60 (1H, dd, J=3Hz, J=7Hz), 7.37 (1H, d, J=2.5Hz), 7.48 (1H, d, J=2.5Hz) 10.40 (1H, br s).

LC/MS t=4.27 min [MH^+] 530.

c) 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid

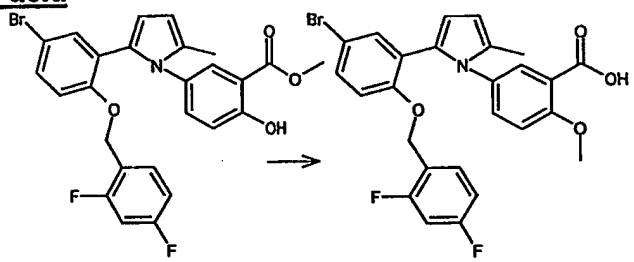


3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid methyl ester (180mg, 0.3mmol) was heated at 60°C in MeOH (3mL) and 2M NaOH (2mL) for 1 hour. Upon cooling, the solvent volume was reduced to approximately 1.5mL then diluted with water to approximately 10mL and neutralised with 2M HCl (2mL). The solution was extracted with EtOAc (10mL), dried ($MgSO_4$), filtered and evaporated to give the title compound (45mg, 26%).

^1H NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 4.81 (2H, s), 6.10 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.59 (1H, d, J=9Hz), 6.75-6.88 (3H, m), 6.97-7.05 (1H ,m), 7.07-7.12 (1H, dd, J=2.5Hz, J=6Hz), 7.21-7.26 (1H, dd, J=2.5, J=6Hz), 7.36 (1H, d, J=2.5Hz), 7.54 (1H, d, J=2.5Hz).

LC/MS t=4.67 min [MH^+] 514

Example 314: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5methyl-pyrrol-1-yl}-6-methoxy-benzoic acid



3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid methyl ester (260mg, 0.4mmol) was dissolved in DMF (3mL) and treated with sodium hydride (60% suspension) (100mg, 2.4mmol) followed by methyl iodide (0.1mL, 1.6mmol).

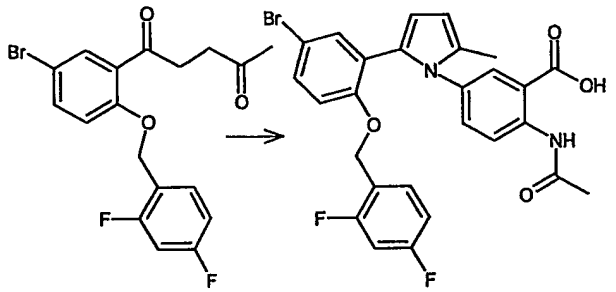
The reaction was stirred under nitrogen at room temperature for 2 hours then water (3mL) was added and stirring continued at room temp overnight. The mixture was further diluted with water (20mL) extracted with DCM (20mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The residue was purified on a Water's sep-pack cartridge (10g) with Et_2O/iso-hexane to give the title compound (150mg, 56%).
^1H NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 4.06 (3H, s), 4.81 (2H, s), 6.09 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.59 (1H, d, J=9Hz), 6.76-6.84 (2H, m), 6.90 (1H, d, J=9Hz) 7.03-7.11 (1H, m), 7.11-7.16 (1H, dd, J=2.5Hz, J=6Hz), 7.19-7.24 (1H, dd, J=2.5, J=6Hz), 7.31 (1H, d, J=2.5Hz), 7.93 (1H, d, J=2.5Hz).
LC/MS t=3.93 min [MH^+] 530.

Example 315: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetyl-amino-benzoic acid

a) 2-(Acetyl-amino)-5-amino-benzoic acid methyl ester

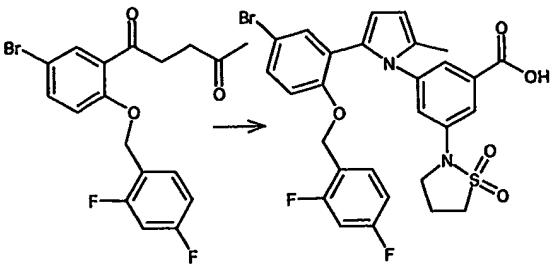
2-(acetyl-amino)-5-nitro-benzoic acid methyl ester (1.000g, 4.2mmol) in was stirred in MeOH (20mL) under a hydrogen atmosphere with with palladium on charcoal (5% wet) at room temperature and pressure for 3 hours. The reaction mixture was then filtered through celite and evaporated to give the title compound (0.85g, 98%).
^1H NMR (400MHz, $CDCl_3$) 2.19 (3H, s), 3.90 (3H, s), 6.90 (1H, dd, J=3Hz, J=6Hz), 7.33 (1H, d, J=3Hz), 8.47 (1H, d, J=9Hz), 10.70 (1H,s).

b)3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetyl-amino-benzoic acid



This compound was synthesised and purified in the same way as 3{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid using the appropriate amine to give the title compound (220mg, 83%).
^1H NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 2.24 (3H, s), 4.76 (2H, s), 6.11 (1H, d, J=3Hz) 6.26 (1H, d, J=3Hz), 6.58 (1H, J=9Hz), 6.74-6.83 (2H, m), 6.96-7.04 (1H, m), 7.14-7.18 (1H, dd, J=2.5, J=6.5Hz), 7.21-7.26 (1H, dd, J=2.5, J=6.5Hz), 7.39 (1H, d, J=2.5Hz), 7.73 (1H, d, J=2.5Hz), 8.61 (1H, d, J=9Hz) 11.00 (1H, s).
LC/MS t=4.13 mins [MH^+] 557.

Example 316: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid

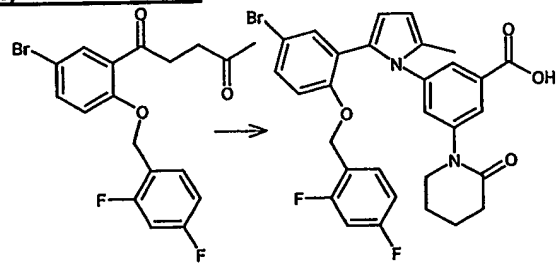


1-[5-Bromo-2-(2,4-difluorobenzyloxy)-phenyl]pentane-1,4-dione (200mg, 0.5mmol), 3-amino-5-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-benzoic acid -methyl ester (140mg, 0.5mmol), pTSA (cat) and powdered 4A molecular sieves (1.0g) were heated NMP (2.5mL) at 180°C. for 18 hours, cooled to room temperature, diluted with EtOAc (15mL), filtered through celite and washed with EtOAc (5mL). The filtrate was then washed with water (20mL), dried ($MgSO_4$), filtered and evaporated. The residue was purified on a Water's sep-pack (10g) with Et_2O/iso-hexane to give the intermediate ester. The title compound was then obtained by heating the ester in MeOH and 2N NaOH at 60°C for 1 hour. Upon cooling, work up gave the title compound (150mg, overall 50%).

^{1}H NMR (400MHz,$CDCl_3$) 2.20(3H,s),2.46-2.54(2H,m),3.35(2H,t,J=7.5Hz), 3.57(2H,t,J=6.5Hz),6.13(1H,d,J=3.0Hz),6.27(1H,d,J=3.0Hz),6.58(1H,d,J=9.0Hz), 6.72-6.83(2H,m),6.94-7.02(1H,m),7.19(1H,t,J=2.0Hz),7.4(1H,dd,J=3,7Hz), 7.39(1H,d,J=3.0Hz),7.5(1H,t,J=1.5Hz),7.73(1H,t,J=1,5Hz)

LC/MS t -3.81 mins [MH+].618.9

Example 317: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)phenyl]-5methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid



This compound was synthesised and purified in the same way as 3-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-benzoic acid using the appropriate amine to give the title compound (100mg, overall 33%).

^{1}H NMR (400MHz,$CDCl_3$) 1.83-1.94 (4H, m), 2.20 (3H, s), 2.50-2.57 (2H, m), 3.26-3.33 (2H, m), 4.74 (2H, s), 6.11 (1H, d, J=4Hz), 6,28 (1H, d, J=4Hz), 6.57 (1H, d, J=9Hz), 6.72-6.84 (2H, m), 6.97-7.07 (2H, m), 7.22 (1H, d, J=3.5Hz), 7.36 (1H, d, J=3Hz), 7.58 (1H, t, J=1.5Hz), 7.85 (1H, t, J=1.5Hz).

LC/MS t=3.88 min [MH^+] 597.

Example 318: 3-{2-[5Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-methylamino-benzoic acid

a) 3-Methylamino-5-nitro-benzoic acid methyl ester

3-Amino-5-nitro-benzoic acid (4.000g, 22mmol), potassium carbonate (8.000g) treated and dimethyl sulphate (4.6ml, 48mmol) were heated at 80°C in NMP (25mL) for 3 hours. The mixture was then cooled, filtered through celite and the residues were washed with DCM (50ml). The filtrate was evaporated to a thick oil which was dissolved in EtOAc (200mL) and washed with .880 ammonia (100mL)/water(100mL). The organic layer was dried, filtered and revaporated to give an oil which was chromatographed on silica gel with Et_2O/iso-hexane to give the title compound (1.600g,35%).

^1H NMR (400MHz,$CDCl_3$) 2.95 (3H, d, J=5Hz), 3.95 (3H, s), 7.51-7.56 (2H,m), 8.14 (1H, t, J=2Hz).

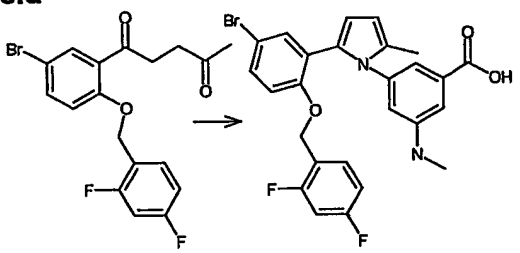
b) 3-Amino-5-methylamino-benzoic acid-methyl ester

3-Methylamino-5-nitro-benzoic-acid-methyl ester (2.200g,10mmol) stirred under a hydrogen atmosphere in MeOH (100mL) with 10% palladium on charcoal (0.8g) for 3 hours at 50°C and 50 psi.The reaction mixture was filtered through celite and evaporated. The residue was purified by chromatography on silica gel with Et_2O containing MeOH (0-10%), as eluant, to give the title compound (0.790g, 42%).

^1H NMR (400MHz,$CDCl_3$) 2.84 (3H, s), 3.87 (3H, s), 6.11 (1H, t, J=4Hz), 6.73 (2H, t, J=4Hz).

LC/MS t=1.20 mins [MH+] 181.

c) 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-methylamino-benzoic acid

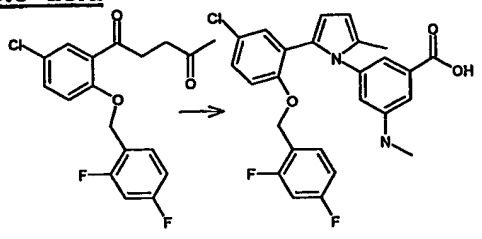


This compound was synthesised and purified in the same way as 3{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid using the appropriate amine to give the title compound (100mg, 38%).

^1H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 2.69 (3H, s), 4.79 (2H, s), 6.11 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.36 (1H, t, J=2Hz), 6.58 (1H, d, J=9Hz), 6.72-6.84 (2H, m), 6.98-7.07 (1H, m), 7.13 (1H, t, J=1.5Hz), 7.18 (1H, t, J=1.5Hz), 7.21 (1H, dd, J= 2Hz, J=6Hz), 7.37 (1H, d, J=2Hz).

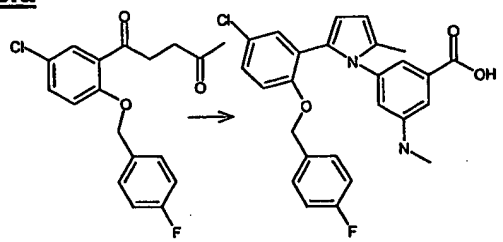
LC/MS t=3.92 min [MH^+] 529.

Example 319: 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-methylamino-benzoic- acid



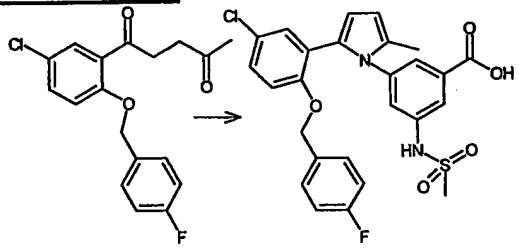
This compound was synthesised and purified in the same way as 3-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-methylamino-benzoic acid using the appropriate amine to give the ttle compound (62 mg, overall 25%).
^{1}H NMR (400MHz, $CDCl_3$) 2.19 (3H, s), 2.69 (3H, s), 4.79 (2H, s), 6.11 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.36 (1H, t, J=2Hz), 6.63 (1H, d, J=8Hz), 6.72-6.83 (2H, m), 6.99-7.11 (2H, m) 7.18 (1H, t, J=2Hz), 7.17 (1H, t, J=2Hz), 7.22 (1H, d, J=2Hz).
LC/MS t=3.70 min [MH^+] 483

Example 320: 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-methylamino-benzoic acid



This compound was synthesised and purified in the same way as 3-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-methylamino-benzoic acid using the appropriate amine to give the title compound (54mg, 23%).
^{1}H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 2.67 (3H, s), 4.74 (2H, s), 6.12 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.35 (1H, t, J=2Hz), 6.58 (1H, d, J=8Hz), 6.93-7.02 (2H, m), 7.03-7.11 (3H, m) 7.13 (1H, br s), 7.17 (1H, br s), 7.23 (1H, d, J=3Hz).
LC/MS t=3.86 min [MH^+] 465.

Example 321: 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-methanesulfonylamido-benzoic acid



Prepared in the same way as 3-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-propionylamino-benzoic acid using the appropriate amine, to give the title compound (54mg, 23%).
^{1}H NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 2.70 (3H, s), 4.74 (2H, s), 6.14 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.62 (1H, d, J=9Hz), 6.93-7.10 (5H, m), 7.13-7.21 (2H, m), 7.23 (1H, d, J=2Hz), 7.57 (1H, br s) .7.74 (1H, br s).
LC /MS t =3.71 min [MH^+] 493

Example 322: 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-chloro-benzoic acid

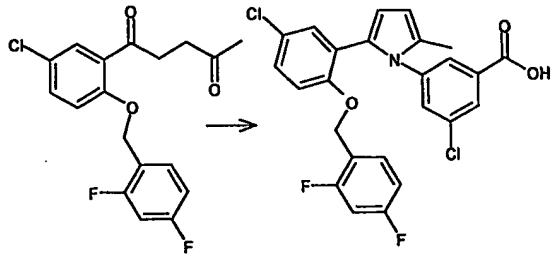
a) 3-Amino-5-chloro benzoic acid

3-Chloro-5-nitro-benzoic acid (1.590g, 7.9mmol) was stirred under a hydrogen atmosphere in ethanol (40mL) with raney-nickel, (aqueous suspension, ~0.4g) at room temperature and pressure for 18 hours. The reaction mixture was then filtered through celite and evaporated to give the title compound (1.300g, 96%).

^{1}H NMR (400MHz, $CDCl_3$) 6.86 (1H, s), 7.18 (1H, s), 7.22 (1H, s).

LC/MS t=2.30 mins [MH^-]170.

b) 3-{2-[5-Chloro-2-(2,4-di-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-5-chloro-benzoic acid

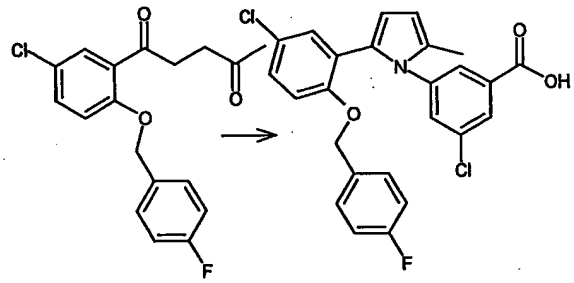


1-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl] pentane-1,4-dione (176mg, 0.5mmol) was heated at reflux in toluene (2.0 mL), containing NMP (0.5mL), with 3-amino-5-chloro-benzoic acid (86mg, 0.5mmol), pTSA (cat.) and powdered 4A molecular sieves (0.8mg) for 18 hours. Upon cooling, the mixture was filtered through celite and washed with EtOAc (10mL). The filtrate was washed with brine, dried ($MgSO_4$), filtered and evapoated to an oil which was purified on a Water's sep-pack (10g) with Et_2O/iso-hexane to give the title compound (170mg, 70%).

^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.75 (2H, s), 6.13 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.66 (1H, d, J=9Hz), 6.73-6.87 (2H, m), 6.98-7.06 (1H, m), 7.10-7.19 (2H, m), 7.25 (1H, s), 6,60 (1H, br s), 7.93 (1H, br s).

LC/MS t=4.40 min [MH^+] 488.

Example 323: 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl[5-methyl-pyrrol-1-yl}-5-chloro-benzoic acid

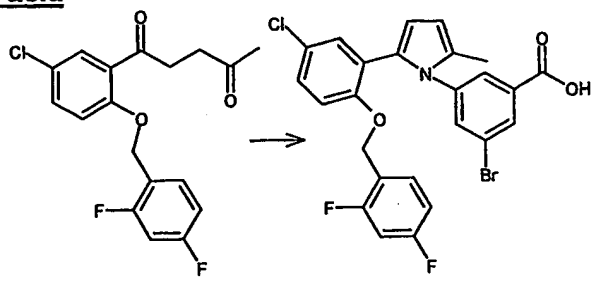


This compound was synthesised and purified in the same way as 3-{2-[5-chloro-2-(2,4-di-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-5-chloro-benzoic acid using the appropriate amine to give the title compound (150mg, 64%).

^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.68 (2H, s), 6.13 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.62 (1H, d, J=9Hz), 6.94-7.15 (6H, m), 7.27 (1H, d, J=2Hz), 7.57 (1H, br s), 7.91 (1H, br s).

LC/MS t=4.00 min [MH^+]470.

Example 324: 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-bromo-benzoic acid

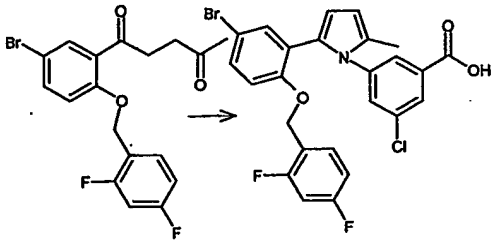


This compound was synthesised and purified in the same way as 3-{2-[5-chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-5-chloro-benzoic acid using the appropriate amine to give the title compound (75mg, 29%).

^{1}H NMR (400MHz, $CDCl_3$) 2.16 (3H, s), 4.75 (2H, s), 6.13 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.66 (1H, d, J=9Hz), 6.74-6.86 (2H, m), 6.97-7.05 (1H, m), 7.13 (1H, dd, J=2Hz, J=6Hz), 7.26 (1H, s), 7.32 (1H, t, J=2Hz), 7.63 (1H, t, J=1.5Hz), 8.10 (1H, t, J=1.5Hz).

LC/MS t=4.10 mins [MH^+] 534

Example 325: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-chloro-benzoic acid

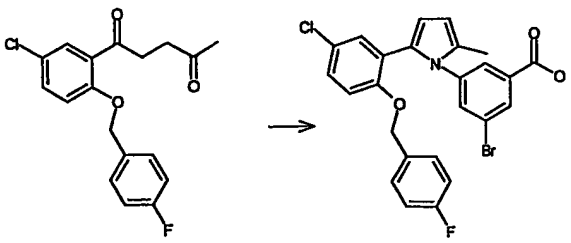


This compound was synthesised and purified in the same way as 3-{2-[5-chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-5-chloro-benzoic acid using the appropriate amine to give the title compound (70mg, 26%).

^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 4.75 (2H, s), 6.13 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.61 (1H, d, J=9Hz), 6.74-6.85 (2H, m), 6.97-7.06 (1H, m) 7.16 (1H, t, J=2Hz), 7.24-7.30 (2H, m), 7.39 (1H, d, J=2Hz), 7.59 (1H, t, J=1.5Hz).

LC/MS t=4.10 mins[MH^+] 534.

Example 326: 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-bromo-benzoic acid



This compound was synthesised and purified in the same way as 3-{2-[5-chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-5-chloro-benzoic acid using the appropriate amine to give the title compound (80mg, 31%).

^{1}H NMR (400MHz, $CDCl_3$) 2.15(3H, s), 4.68 (2H, s), 6.13 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.61 (1H, d, J=8Hz), 6.94-7.14 (5H,m), 7.24-7.32 (2H,m), 7.61 (1H, br s), 8.60 (1H, br s).
LC/MS t =4.32 min [MH^+]516.

Example 327: 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-morpholino-4-yl-benzoic acid

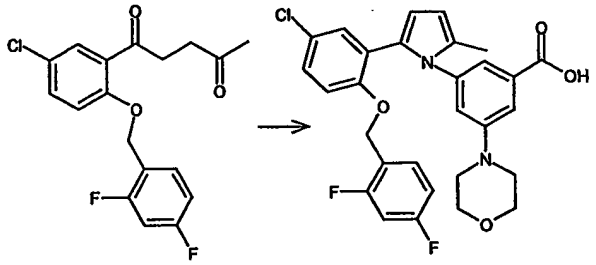
a) 3-Morpholino-5-nitro-benzoic acid

3-Bromo-5-nitro-benzoic acid (4.000g, 16.3mmol), cesium carbonate, (8g, 2.46mmol), tris(dibenzylideneacetone) dipalladium (0) (60mg, 0.065mmol), xantphos (116mg, 0.2mmol) and morpholine (2.1ml, 24mmol) were heated at reflux in dioxan (40mL) under nitrogen for 92 hours. The reaction mixture was then evaporated to an oil. Upon addition of DCM (~400ml) a precipitate formed. The precipitate was removed by filtration and the dissolved in MeOH/DCM (20/40mL), adsobed onto silica gel (25g) and chromatographed on silica gel with DCM-10% AcOH in MeOH to give the title compound (2.500g, 61%).
^{1}H NMR (400MHz, $CDCl_3$) 3.30 (4H ,t, J=5Hz), 3.86 (4H, t, J=5Hz), 7.91 (2H, d, J=8Hz) 8.18 (1H, s).
LC/MS t=2.60 min [MH^+] 253.

b) 3-Amino-5-morpholino-benzoic acid

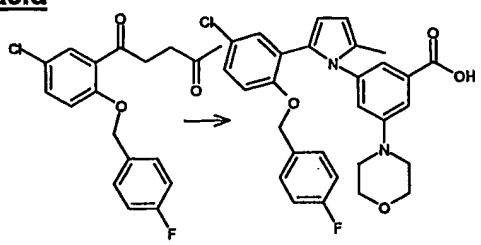
3-Morpholino-5-nitro-benzoic acid (2.500g, 9.9mmol) was heated at 50°C and 50.lb./sq.inch under a hydrogen atmosphere in MeOH (100mL) with raney-nickel (~0.5g) for 25 hours. The reaction mixture was then filtered through celite and evaporated. Trituation with ether/iso-hexane (10/40ml) gave the title compound (1.500g,77%).
^{1}H NMR (400MHz, $CDCl_3$) 3.12 (4H, t, J=8Hz), 3.82 (4H, t, J=8Hz), 6.55 (1H, s), 6.91 (1H, s), 6.97 (1H, s).
LC/MS t=1.40 min [MH^+] 223.

c) 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-l-yl}-5-morpholino-4-yl-benzoic acid



This compound was synthesised and purified in the same way as 3-{2-[5-chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-5-chloro-benzoic acid using the appropriate amine to give the title compound (120mg, 45%).
^{1}H NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 2.94 (4H, t, J=5Hz), 3.76 (4H, t, J=5Hz), 4,75 (2H, s), 6.13 (1H, d, J=3Hz), 6.23 (1H, d, J=3Hz), 6.58-6.67 (2H, m), 6.73-6.84 (2H, m), 6.96-7.05 (1H, m), 7.09 (1H, dd, J=2Hz, J=6Hz), 7.23 (1H, d, J=2Hz), 7.29 (1H, br s), 7.47 (1H, br s).
LC/MS t=3.70 min [MH+] 539.

Example 328: 3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-morpholin-4-yl-benzoic-acid



This compound was synthesised and purified in the same way as 3-{2-[5-chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-5-chloro-benzoic acid using the appropriate amine to give the title compound (100mg, 38%).
^{1}H NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 2.91 (4H, t, J=5Hz), 3.75 (4H, t, J=5Hz) 6.13 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.58 (1H, d, J=8Hz), 6.64 (1H, br s), 6.93-7.10 (5H, m), 7.22-7.32 (2H ,m), 7.46 (1H,br s).
LC/MS t=3.70 min [MH^+]521.

Example 329: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-ethyl-pyrrol-1-yl}-benzoic acid

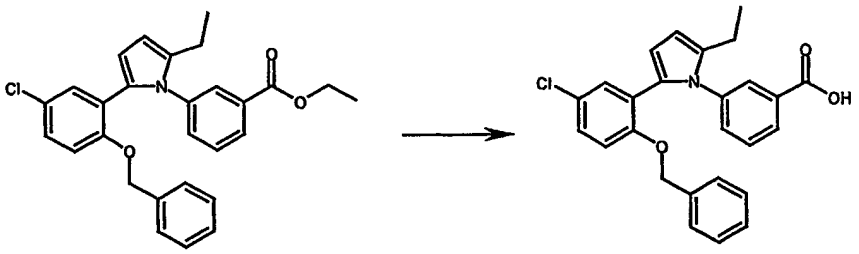
a) 1-[5-Chloro-2-(benzyloxy)-phenyl]-hexane-1,4-dione

A mixture of 5-chloro-2-benzyloxy-benzaldehyde (1.003g, 4.07mmol), ethyl vinyl ketone (0.61ml), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (161mg) and triethylamine (0.85ml) was heated in ethanol (1.4ml) at reflux for 5 hours. Upon cooling, the mixture was diluted with EtOAc and washed sequentially with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4) filtered and concentrated. The residue was purified by chromatography with iso-hexane containg a gradient of EtOAc (5-10%) to give the title compound (0.707g, 52%).
^{1}H NMR (400MHz, $CDCl_3$) 1.06 (3H, t, J=7Hz), 2.47 (2H, q, J=7Hz), 2.75 (2H, t, J=7Hz), 3.24 (2H, t, J=7Hz), 5.15 (2H, s), 6.95 (1H, d, J=9Hz), 7.20-7.50 (6H, m's excess), 7.67-7.75 (1H, m).

b) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-ethyl-pyrrol-1-yl}-benzoic acid ethyl ester

1-[5-Chloro-2-(benzyloxy)-phenyl]-hexane-1,4-dione (306mg, 0.92mmol), ethyl-3-aminobenzoate (0.17ml, 1.10mmol) and pTSA (cat) were heated in toluene (9ml) at reflux for 24 hours. Upon cooling, the mixture was diluted with EtOAc and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography with hexane containing a gradient of EtOAc (2-3%), as eluant, to give the title compound (233mg, 55%).
^{1}H NMR (400MHz, $CDCl_3$) 1.15 (3H, t, J=8Hz), 1.30 (3H, t, J=8Hz), 2.47 (2H, t, J=8Hz), 4.28 (2H, q, J=7Hz), 4.74 (2H, s), 6.16 (1H, d, J=3Hz), 6.34 (1H, d, J=3Hz), 6.53 (1H, d, J=9Hz), 6.98-7.10 (3H, m), 7.11-7.17 (1H, m), 7.20-7.33 (5H, m' excess), 7.76 (1H, s), 7.91 (1H, d, J=8Hz).

c) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-ethyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-ethyl-pyrrol-1-yl}-benzoic acid ethyl ester (233mg) was heated in EtOH (5ml) and 2M NaOH (2.5ml) at reflux for 2 hrs. The mixture was cooled to room temperature and diluted with EtOAc, washed with 2M HCl then dried (Na_2SO_4), filtered and evaporated to give the title compound.
LC/MS t=4.05 min [MH+] 432, 434; [MH-] 430, 432.

Example 330: 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-ethyl-pyrrol-1-yl}-benzoic acid

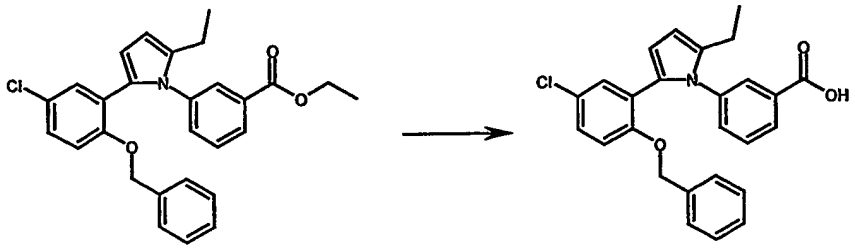
a) 1-[5-Bromo-2-(benzyloxy)-phenyl]-hexane-1,4-dione

A mixture of 5-bromo-2-benzyloxy-benzaldehyde (1.059g, 3.64mmol), ethyl vinyl ketone (0.54ml), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (173mg) and triethylamine (0.76ml) was heated in ethanol (1.2ml) at reflux for 5 hours. Upon cooling, the mixture was diluted with EtOAc and washed sequentially with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4) filtered and concentrated. The residue was purified by chromatography with iso-hexane containg a gradient of EtOAc (5-10%) to give the title compound (0.813g).
^1H NMR (400MHz, $CDCl_3$) 1.05 (3H, t, J=7Hz), 2.47 (2H, q, J=7Hz), 2.74 (2H, t, J=7Hz), 3.24 (2H, t, J=7Hz), 5.14 (2H, s), 6.90 (1H, d, J=9Hz), 7.20-7.56 (6H, m's excess), 7.82-7.88 (1H, m).

b) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-ethyl-pyrrol-1-yl}-benzoic acid ethyl ester

1-[5-Bromo-2-(benzyloxy)-phenyl]-hexane-1,4-dione (390mg, 1.04mmol), ethyl-3-aminobenzoate (0.19ml) and pTSA (cat) were heated in toluene (10.4ml) at reflux for 24 hours. Upon cooling, the mixture was diluted with EtOAc and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography with hexane containing a gradient of EtOAc (2-3%) as eluant, to give the title compound (294mg, 57%).
^1H NMR (400MHz, $CDCl_3$) 1.15 (3H, t, J=7Hz), 1.31 (3H, t, J=7Hz), 2.47 (2H, q, J=7Hz), 4.28 (2H, q, J=7Hz), 4.73 (2H, s), 6.16 (1H, d, J=3Hz), 6.34 (1H, d, J=3Hz), 6.48 (1H, d, J=9Hz), 7.00-7.07 (2H, m), 7.10-7.20 (2H, m), 7.22-7.33 (4H, m' excess), 7.38 (1H, s), 7.76 (1H, s), 7.91 (1H, d, J=8Hz).

c) 3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-ethyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-ethyl-pyrrol-1-yl}-benzoic acid ethyl ester (233mg) was heated in EtOH (6ml) and 2M NaOH (3ml) at reflux for 2 hrs. The mixture was cooled to room temperature and diluted with EtOAc, washed with 2M HCl then dried (Na_2SO_4), filtered and evaporated to give the title compound.

LC/MS t=4.08 min [MH+] 476, 478; [MH-] 474, 476.

Example 331: 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid

a) 5-Methyl-2-(4-fluoro-benzyloxy)-benzaldehyde

5-Methyl-2-hydroxy-benzaldehyde (5.000g, 36.8mmol), K_2CO_3 (10.212g) and 4-fluorobenzyl bromide (4.81mL, 38.61mmol) were heated at reflux in acetone (37mL) for 1.75hrs. Upon cooling to room temperature, the residue was diluted with acetone, filtered and evaporated. The residue was dissolved in Et_2O, washed with water, dried (Na_2SO_4), filtered and evaporated to give the title compound.

^{1}H NMR (400MHz, $CDCl_3$) 2.31 (3H, s), 5.12 (2H, s), 6.93 (1H, d, J-6.9Hz), 7.02-7.15 (2H, m), 7.34 (1H, dd, J=2Hz, J=9Hz), 7.37-7.45 (2H, m), 7.65 (1H, d, J=9Hz) 10.52 (1H, s).

b) 1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione

A mixture of 5-methyl-2-(4-fluoro-benzyloxy)-benzaldehyde (4.960g, 20.34mmol), methyl vinyl ketone (2.54ml, 30.60mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (837mg) and triethylamine (4.3ml) was heated in ethanol (7.0ml) at reflux for 5 hours. Upon cooling, the mixture was diluted with EtOAc and washed sequentially with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4) filtered and concentrated. The residue was purified by chromatography with iso-hexane containg a gradient of EtOAc (2-15%) to give the title compound (2.108g, 35%).

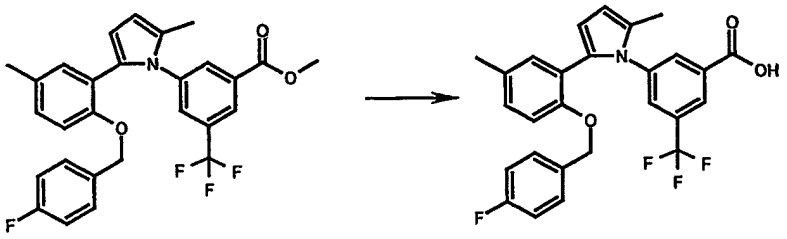
^{1}H NMR (400MHz, $CDCl_3$) 2.19 (3H, s), 2.30 (3H, s), 2.78 (2H, t, J=6Hz), 3.22 (2H, t, J=6Hz), 5.10 (2H, s), 6.89 (1H, d, J=9Hz), 7.05-7.13 (2H, m), 7.23 (1H, dd, J=2Hz, J=9Hz), 7.38-7.47 (2H, m), 7.53 (1H, d, J=2Hz).

c) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester

1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (110mg), 3-amino-5-trifluoromethyl-benzoic acid methyl ester (96mg) and pTSA (cat) were heated in NMP at 150°C in a microwave for 10 minutes. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (3-6%) to give the title compound.

LC/MS t=4.28 min, [MH^+] 498.

d) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid



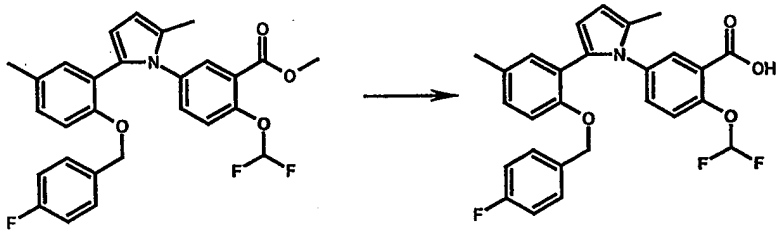
3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester (76mg) was heated at 120°C in a microwave in a mixture of EtOH (1.6mL) and 2M NaOH (0.8mL) for 3 minutes. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated. The residue was purified by MDAP to give the title compound (55mg).
LC/MS t=4.19 min, [MH^+] 484; [MH^-] 482.

Example 332: 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid

a) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid methyl ester

1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (107mg), 4-amino-2-difluoromethoxy-benzoic acid methyl ester (76mg) and pTSA (cat) were heated in NMP (1.5mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with Et_2O and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (5-10%) to give the title compound (70mg, 40%).
LC/MS t=3.84 min, [MH^+] 496.

b) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid



3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid methyl ester (70mg) was heated at 120°C in a microwave in a mixture of EtOH (1.4mL) and 2M NaOH (0.7mL) for 3 minutes. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated. The residue was purified by MDAP to give the title compound (47mg).
^{1}H NMR (400MHz, *d*6-DMSO) 2.06 (3H, s), 2.15 (3H, s), 4.75 (2H, s), 6.03 (1H, d, J=3Hz), 6.12 (1H, d, J=3Hz), 6.72 (1H, d, J=9Hz), 6.92-6.98 (2H, m), 6.98-7.38 (7H, m), 7.41 (1H, d, J=2Hz), 13.11 (1H, br).
LC/MS t=3.95 min, [MH^+] 482; [MH^-] 480.

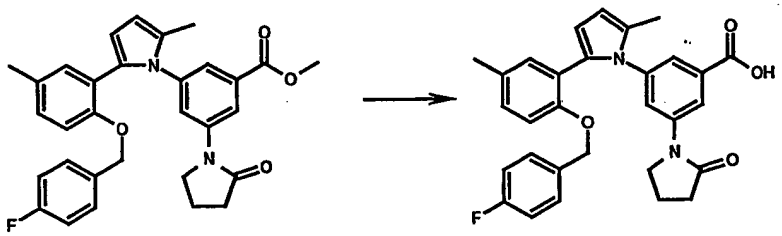
Example 333: 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid

a) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester

1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (104mg), 3-amino-5-(2-oxo-pyrrolidin-1yl)-benzoic acid methyl ester (94mg) and pTSA (cat) were heated in NMP (1.5mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with Et_2O and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (20-50%) to give the title compound (81mg, 45%).

LC/MS t=3.68 min, $[MH^+]$ 513

b) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid



3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (80mg) was heated at 120°C in a microwave in a mixture of EtOH (1.6mL) and 2M NaOH (0.8mL) for 3 minutes. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated. The residue was purified by MDAP to give the title compound.

LC/MS t=3.71 min, $[MH^+]$ 499; $[MH^-]$ 497.

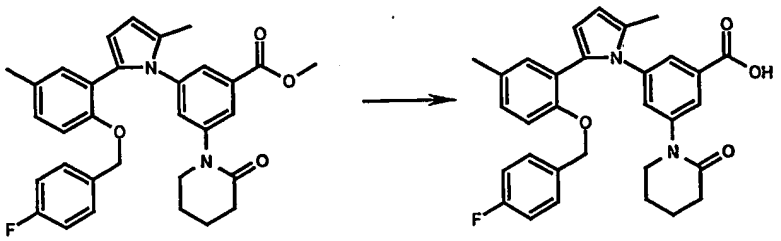
Example 334: 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid

a) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester

1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (107mg), 3-amino-5-(2-oxo-piperidin-1yl)-benzoic acid methyl ester (99mg) and pTSA (cat) were heated in NMP (1.5mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with Et_2O and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (20-50%) to give the title compound (88mg, 46%).

LC/MS t=3.63 min $[MH^+]$ 527

b) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid



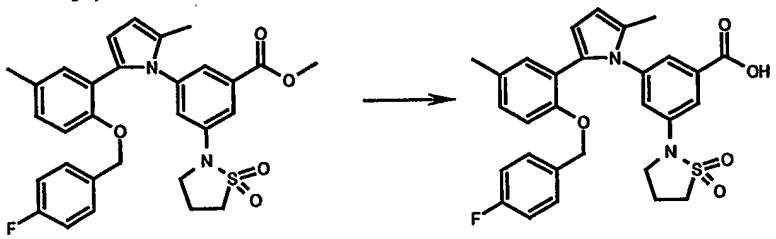
3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (83mg) was heated at 120°C in a microwave in a mixture of EtOH (1.6mL) and 2M NaOH (0.8mL) for 3 minutes. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated. The residue was purified by MDAP to give the title compound (48mg).
LC/MS t=3.67 min, [MH^+] 513; [MH^-] 511.

Example 335: 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-benzoic acid

a) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-benzoic acid methyl ester

1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (110mg), 3-amino-5-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-benzoic acid methyl ester (99mg) and pTSA (cat) were heated in NMP (1.5mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with Et_2O and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (20-50%) to give the title compound (82mg, 41%).
LC/MS t=3.63 min [MH^+] 549

b) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-benzoic acid



3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*iso*thiazolidin-2-yl)-benzoic acid methyl ester (72mg) was heated at 120°C in a microwave in a mixture of EtOH (1.6mL) and 2M NaOH (0.8mL) for 3 minutes. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated. The residue was purified by MDAP to give the title compound (45mg).
LC/MS t=3.68 min, [MH^+] 535; [MH^-] 533.

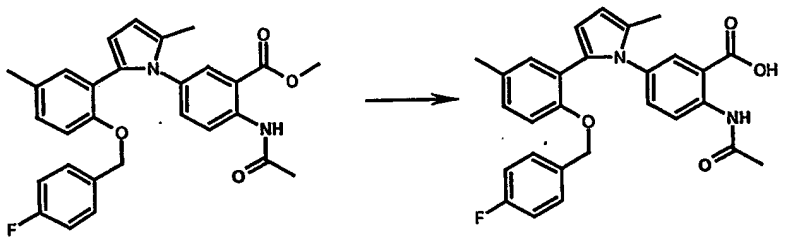
Example 336: 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid

a) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester

1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (110mg), 2-acetylamino-5-amino-benzoic acid methyl ester (76mg) and pTSA (cat) were heated in NMP (1.5mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with Et_2O and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (12-20%) to give the title compound.

LC/MS t=3.76 min [MH^+] 487

b) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid



3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester (82mg) s heated at 120°C in a microwave in a mixture of EtOH (1.6mL) and 2M NaOH (0.8mL) for 3 minutes. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated. The residue was purified by MDAP to give the title compound (46mg).

^1H NMR (400MHz, *d*6-DMSO) 2.05 (3H, s), 2.12 (3H, s), 2.14 (3H, s), 4.78 (2H, s), 6.01 (1H, d, J=3Hz), 6.71 (1H, d, J=8Hz), 6.90-6.98 (2H, m), 7.07-7.25 (6H, m), 7.56 (1H, d, J=2Hz), 8.33 (1H, d, J=9Hz), 11.11 (1H, br).

LC/MS t=3.62 min, [MH^+] 431; [MH^-] 429.

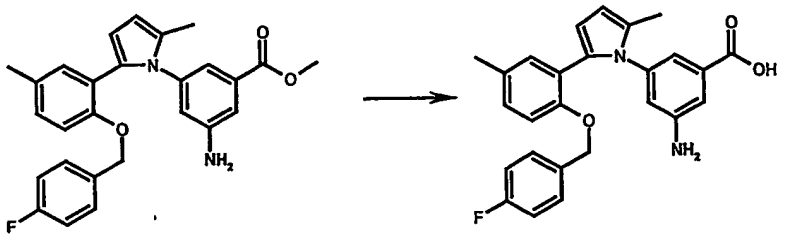
Example 337: 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid

a) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester

1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (608mg), 3,5-diamino-benzoic acid methyl ester (387mg) and pTSA (cat) were heated in NMP (4mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (12-20%) to give the title compound (478mg, 50%).

LC/MS t=3.63 min [MH^+] 445

b) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid



3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester (82mg) was heated at 120°C in a microwave in a mixture of EtOH (1.6mL) and 2M NaOH (0.8mL) for 3 minutes. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated. The residue was purified by MDAP to give the title compound.

^{1}H NMR (400MHz, *d*6-DMSO) 2.59 (3H, s), 2.65 (3H, s), 5.37 (2H, s), 6.53 (1H, d, J=3Hz), 6.64 (1H, d, J=3Hz), 7.17 (1H, s), 7.26 (1H, d, J=9Hz), 7.39-7.50 (3H, m), 7.62-7.82 (5H, m).

LC/MS t=3.62 min, [MH^+] 431; [MH$^-$] 429.

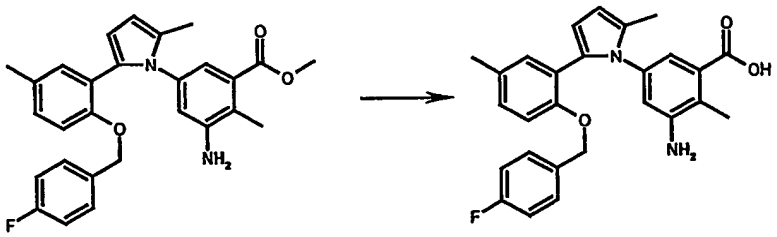
Example 338: 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid

a) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid methyl ester

1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione (250mg), 3,5-diamino-2-methyl-benzoic acid methyl ester (163mg) and pTSA (cat) were heated in NMP (3.4mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (12-20%) to give the title compound (164mg, 43%).

LC/MS t=3.67 min [MH^+] 249

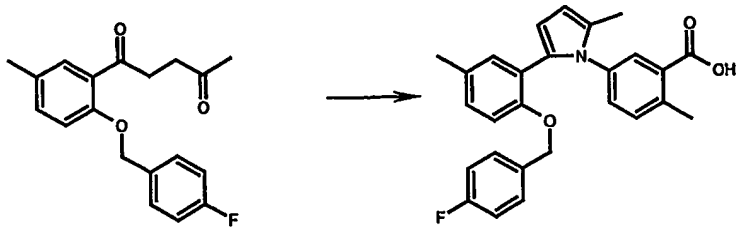
b) 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid



3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-diamino-6-methyl-benzoic acid methyl ester (101mg) was heated at 120°C in a microwave in a mixture of EtOH (2.0mL) and 2M NaOH (1.0mL) for 3 minutes. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated. The residue was purified by MDAP to give the title compound.

LC/MS t=3.64 min, [MH^+] 445; [MH$^-$] 443.

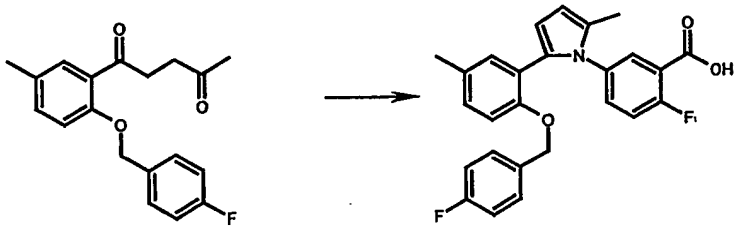
Example 339: 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid



1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione, 5-amino-2-methyl-benzoic acid and pTSA (cat) were heated in NMP at 150°C in a microwave for 10 minutes. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and water, dried (Na_2SO_4), filtered and concentrated. The residue was purified by MDAP to give the title compound.

LC/MS t=3.96 min [MH^+] 430, [MH^-] 428

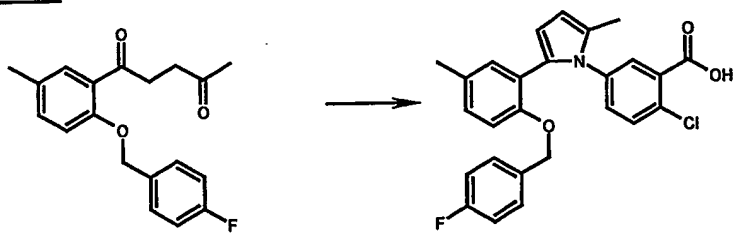
Example 340: 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid



1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione, 5-amino-2-fluoro-benzoic acid and pTSA (cat) were heated in NMP at 150°C in a microwave for 10 minutes. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and water, dried (Na_2SO_4), filtered and concentrated. The residue was purified by MDAP to give the title compound.

LC/MS t=3.95 min [MH^+] 434, [MH^-] 432

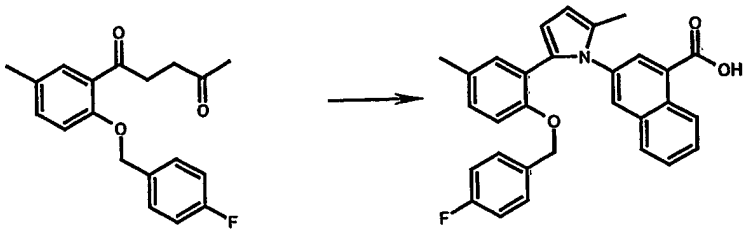
Example 341: 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid



1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione, 5-amino-2-chloro-benzoic acid and pTSA (cat) were heated in NMP at 150°C in a microwave for 10 minutes. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and water, dried (Na_2SO_4), filtered and concentrated. The residue was purified by MDAP to give the title compound.

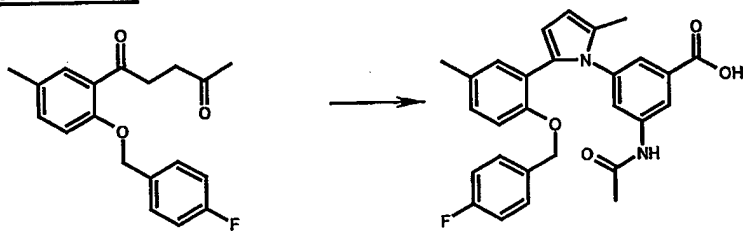
^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 2.25 (3H, s), 4.67 (2H, s), 6.13 (1H, d, J=3Hz), 6.25 (1H, d, J=4Hz), 6.56 (1H, d, J=8Hz), 6.91-7.07 (6H, m), 7.11 (1H, m, J=2Hz), 7.23 (1H, s), 7.63 (1H, d, J=2Hz).
LC/MS t=4.14 min [MH^+] 450, [MH^-] 448

Example 342: 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-1-naphthoic acid



1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione, 3-amino-naphthalene-1-carboxylic acid and pTSA (cat) were heated in NMP at 150°C in a microwave for 10 minutes. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and water, dried (Na_2SO_4), filtered and concentrated. The residue was purified by MDAP to give the title compound.
LC/MS t=4.12 min [MH^+] 466, [MH^-] 464

Example 343: 3-{2-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-acetylamino-benzoic acid



1-[5-Methyl-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione, 3-acetylamino-5-amino-benzoic acid and pTSA (cat) were heated in NMP at 150°C in a microwave for 10 minutes. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and water, dried (Na_2SO_4), filtered and concentrated. The residue was purified by MDAP to give the title compound.
LC/MS t=3.61 min [MH^+] 473, [MH^-] 471

Example 344: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid

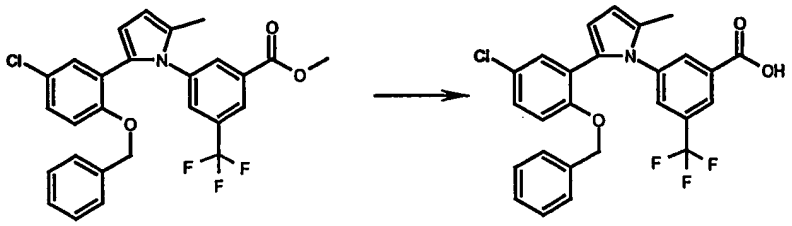
a) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester

1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (104mg), 3-amino-5-trifluoromethyl-benzoic acid methyl ester (85mg) and pTSA (cat) were heated in NMP (1.5mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with Et_2O and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The

residue was purified on silica gel with iso-hexane containing EtOAc (5%) to give the title compound (70mg)

LC/MS t=4.02 min, [MH^+] 500, 502.

b) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid



3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-trifluoromethyl-benzoic acid methyl ester (105mg) was heated at reflux in a mixture of EtOH (2.0mL) and 2M NaOH (1.0mL) for 2.5 hours. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated to give the title compound.

LC/MS t=4.32 min, [MH^+] 486, 488; [MH^-] 484, 486.

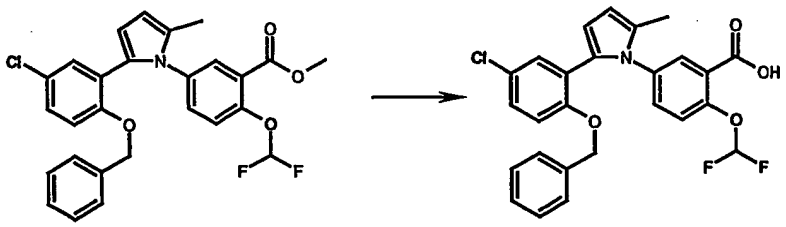
Example 345: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid

a) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid methyl ester

1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (112mg), 5-amino-2-difluoromethoxy-benzoic acid methyl ester (126mg) and pTSA (cat) were heated in NMP (1.5mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with Et_2O and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (5-10%) to give the title compound (121mg)

LC/MS t=4.11 min, [MH^+] 498, 500

b) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid



3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid methyl ester (117mg) heated at reflux in a mixture of EtOH (3.0mL) and 2M NaOH (1.5mL) for 2 hours. The mixture was diluted with EtOAc and washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound.

^{1}H NMR (400MHz, *d*6-DMSO) 2.15 (3H, s), 4.71 (2H, s), 6.14 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.58 (1H, t, J=74Hz), 6.60 (1H, d, J=9Hz), 7.00-7.15 (5H, m), 7.21-7.34 (4H, m's excess), 7.65-7.69 (1H, m).

LC/MS t=3.75 min, [MH^+] 484, 486; [MH^-] 482, 484.

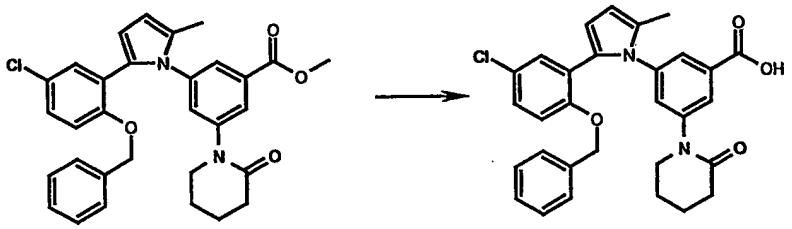
Example 346: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid

a) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester

1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (111mg), 3-amino-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (112mg) and pTSA (cat) were heated in NMP (1.5mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with Et_2O and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (30-80%) to give the title compound (149mg)

LC/MS t=3.87 min, [MH^+] 529, 531

b) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid



3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (144mg) was heated at reflux in a mixture of EtOH (3.0mL) and 2M NaOH (1.5mL) for 2 hours. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated to give the title compound (134mg).

LC/MS t=3.55 min, [MH^+] 515, 517; [MH^-] 513, 515.

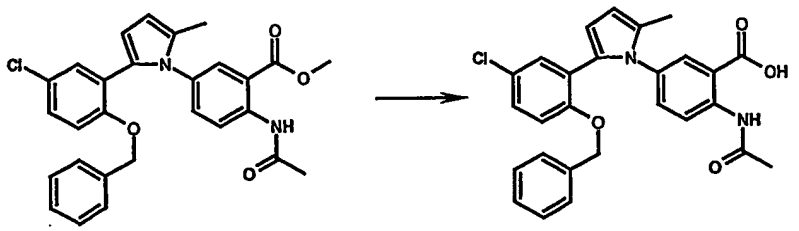
Example 347: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid

a) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester

1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (111mg), 2-acetylamino-5-amino-benzoic acid methyl ester (97mg) and pTSA (cat) were heated in NMP (1.5mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with Et_2O and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (5-30%) to give the title compound (124mg)

LC/MS t=4.03 min, [MH^+] 489, 491

b) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid



3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester (148mg) heated at 120°C in a microwave in a mixture of EtOH (3.0mL) and 2M NaOH (1.0mL) for 3 minutes. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated. The residue was purified by MDAP to give the title compound (46mg).

^{1}H NMR (400MHz, *d*6-DMSO) 2.13 (3H, s), 2.24 (3H, s), 4.76 (2H, s), 6.12 (1H, d, J=3Hz), 6.29 (1H, d, J=4Hz), 6.59 (1H, d, J=9Hz), 7.02-7.12 (3H, m), 7.16 (1H, dd, J=3Hz, J=9Hz), 7.22-7.33 (5H, m's excess), 7.75 (1H, d, J=2Hz), 8.60 (1H, d, J=9Hz), 10.85 (1H, s).

LC/MS t=4.15 min, [MH^+] 475, 477; [MH^-] 473, 475.

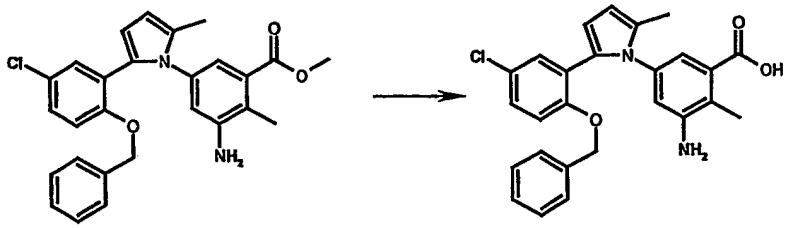
Example 348: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid

a) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid methyl ester

1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (203mg), 3,5-diamino-2-methyl-benzoic acid methyl ester (154mg) and pTSA (cat) were heated in toluene (2.6mL) at reflux for 4hrs. The mixture was diluted with EtOAc and washed sequentially with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (30-50%) to give the title compound (106mg)

LC/MS t=3.94 min, [MH^+] 461, 463

b) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid

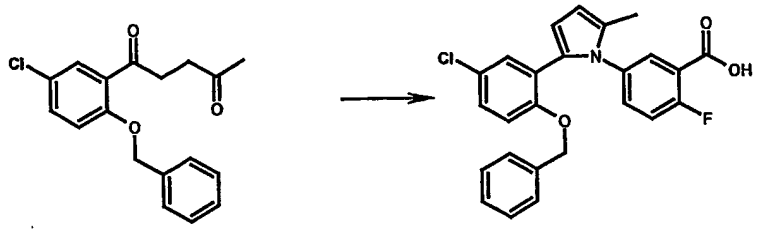


3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-6-methyl-benzoic acid methyl ester (35mg) was heated at reflux in a mixture of EtOH (0.7mL) and 2M NaOH (0.35mL) for 2.5 hours. The mixture was diluted with EtOAc and washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound.

^{1}H NMR (400MHz, *d*6-DMSO) 2.04 (3H, s), 2.21 (3H, s), 4.95 (2H, s), 5.99 (1H, d, J=3Hz), 6.20 (1H, d, J=3Hz), 6.55 (1H, d, J=2Hz), 6.68 (1H, d, J=2Hz), 6.87 (1H, d, J=9Hz), 7.02 (1H, d, J=3Hz), 7.14 (1H, dd, J=3Hz, J=9Hz), 7.18-7.38 (5H, m).

LC/MS t=3.49 min, [MH^+] 447, 449; [MH^-] 445, 447.

Example 349: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid

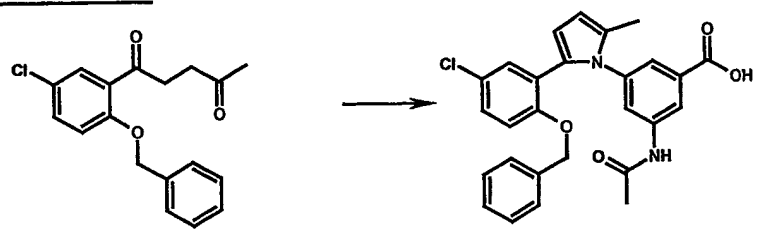


1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (100mg), 5-amino-2-fluoro-benzoic acid and powdered 4A molecular sieves (300mg) were heated in toluene (0.2M solution) at reflux for 24hrs. The mixture was diluted with EtOAc filtered and evaporated. The residue was purified by MDAP, to give the title compound (54mg).

^{1}H NMR (400MHz, $CDCl_3$) 2.14 (3H, s), 4.75 (2H, s), 6.13 (1H, dd, J=1Hz, J=3Hz), 6.29 (1H, J=3Hz), 6.61 (1H, d, J=9Hz), 6.94-7.12 (5H, m), 7.23-7.34 (4H, m's excess), 7.64-7.70 (1H, m).

LC/MS t=3.76 min, [MH^+] 436, 438; [MH^-] 434

Example 350: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-acetylamino-benzoic acid

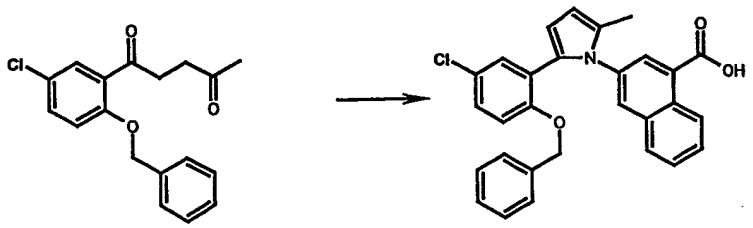


1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (100mg), 3-acetylamino-5-amino-benzoic acid (60mg) and powdered 4A molecular sieves (300mg) were heated in toluene (0.2M solution) at reflux for 24hrs. The mixture was diluted with EtOAc filtered and evaporated. The residue was purified by MDAP, to give the title compound (77mg).

^{1}H NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 2.15 (3H, s), 4.75 (2H, s), 6.13 (1H, J=3Hz), 6.30 (1H, J=3Hz), 6.58 (1H, d, J=9Hz), 6.94-7.13 (4H, m), 7.23-7.37 (4H, m's excess), 7.44 (1H, s), 8.07 (1H, s).

LC/MS t=3.46 min, [MH^+] 475, 477; [MH^-] 473, 475.

Example 351: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-1-napthoic acid

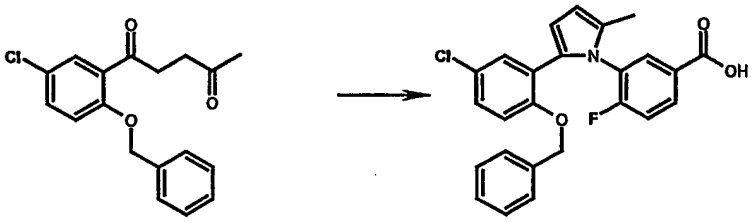


1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (100mg), 3-amino-naphthalene-1-carboxylic acid (71mg) and powdered 4A molecular sieves (300mg) were heated in toluene (0.2M solution) at reflux for 24hrs. The mixture was diluted with EtOAc filtered and evaporated. The residue was purified by MDAP, to give the title compound (113mg).

^{1}H NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 4.65 (2H, s), 6.19 (1H, J=3Hz), 6.35 (1H, J=3Hz), 6.47 (1H, d, J=9Hz), 6.88-6.96 (2H, m), 7.01 (1H, dd, J=2Hz, J=9Hz), 7.12-7.23 (3H, m), 7.38 (1H, d, J=2Hz), 7.48-7.56 (1H, m), 7.60 (1H, d, J=1Hz), 7.61-7.70 (2H, m), 8.10 (1H, d, J=2Hz), 9.03 (1H, d, J=9Hz).

LC/MS t=4.20 min, [MH^+] 468, 470; [MH^-] 466, 468.

Example 352: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-4-fluoro-benzoic acid

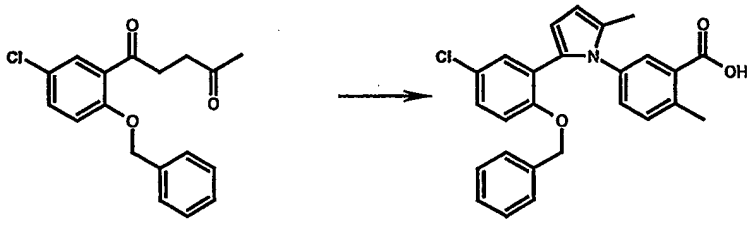


1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (100mg), 3-amino-4-fluoro-benzoic acid (60mg) and powdered 4A molecular sieves (300mg) were heated in toluene (0.2M solution) at reflux for 24hrs. The mixture was diluted with EtOAc filtered and evaporated. The residue was purified by MDAP, to give the title compound (63mg).

^{1}H NMR (400MHz, $CDCl_3$) 2.11 (3H, s), 4.84 (2H, s), 6.16 (1H, dd, J=1Hz, J=3Hz), 6.34 (1H, J=3Hz), 6.56 (1H, d, J=9Hz), 7.02 (1H, dd, J=3Hz, J=9Hz), 7.04-7.15 (2H, m), 7.22 (1H, d, J=2Hz), 7.23-7.32 (4H, m's excess), 7.81 (1H, dd, J=2Hz, J=7Hz), 7.98-8.04 (1H, m).

LC/MS t=3.99 min, [MH^+] 436, 438; [MH^-] 434, 436.

Example 353: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid

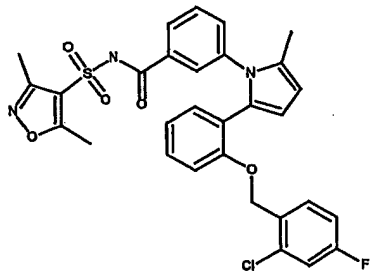


1-[5-Chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione (111mg), 5-amino-2-methyl-benzoic acid (61mg) and pTSA (cat) were heated in NMP (4.5mL) at 150°C for 10 minutes. The mixture was diluted with Et_2O wahed with 2M HCl, dried (Na_2SO_4), filtered and evaporated. The residue was purified by MDAP, to give the title compound (89mg).

^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 2.62 (3H, s), 4.77 (2H, s), 6.13 (1H, d, J=3Hz), 6.30 (1H, J=3Hz), 6.57 (1H, d, J=9Hz), 7.00-7.13 (5H, m), 7.20-7.30 (4H, m's excess), 7.77 (1H, m).

LC/MS t=4.04 min, [MH^+] 432, 434; [MH^-] 430, 432.

Example 354: 3-{2-[2-(2-Chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(3,5-dimethyl-isoxazole-4-sulfonyl)-benzenamide



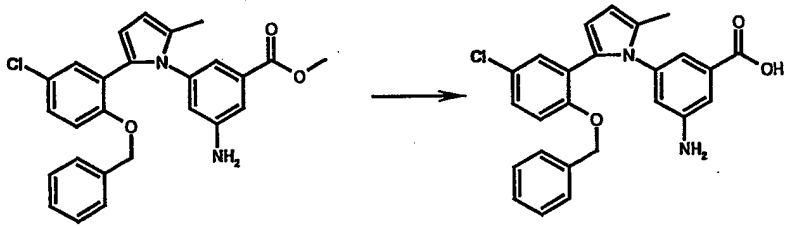
Prepared in the same way as 3-{2-[2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-(3,5-dimethyl-isoxazole-4-sulfonyl)-benzenamide.
LC/MS t=4.55 min, [MH^+] 594, 596; [MH^-] 592, 594.

Example 355: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid

a) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester

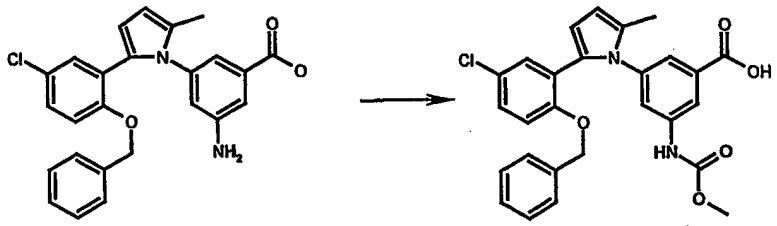
1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (824mg, 2.60mmol), 3,5-diamino-benzoic acid methyl ester (550mg, 3.31mmol) and pTSA (cat) were heated at reflux in toluene (10mL) for 2.5hrs. The mixture was allowed to stand overnight, diluted with EtOAc, and washed sequentially with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and evaporated. The residue was purified by by chromatography on silica gel with iso-hexane containing EtOAc (2-40%) as eluant, to give the title compound (946mg).
LC/MS t=3.89 min, [MH^+] 447, 449.

b) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid



3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester (67mg) was heated at reflux in a mixture of EtOH (1.4mL) and 2M NaOH (0.7mL) for 2.5 hours. The mixture was diluted with EtOAc and washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound.
^1H NMR (400MHz, $CDCl_3$) 2.59 (3H, s), 5.46 (2H, s), 6.56 (1H, d, J=3Hz), 6.78 (1H, d, J=3Hz), 7.18 (1H, s), 7.39-7.48 (2H, m), 7.53 (1H, d, J=2Hz), 7.68 (1H, dd, J=3Hz, J=9Hz), 7.71-7.90 (6H, m's excess).
LC/MS t=3.73 min, [MH^+] 433, 435; [MH^-] 431, 433.

Example 356: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-methoxycarbonylamino-benzoic acid

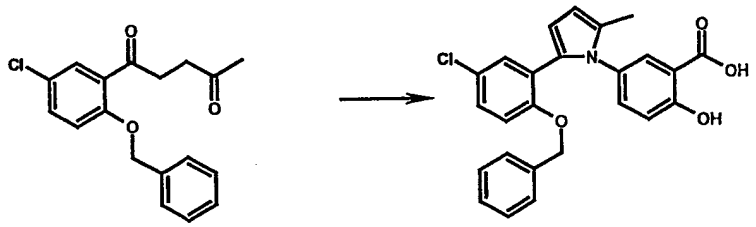


Methyl chloroformate was added dropwise to a solution of 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid and DMAP (cat) in DCM-pyridine (1:1, 2mL). The mixture was stirred at room temperature for 2.5hrs then allowed to stand to 6 days then diluted with DCM and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified by MDAP to give the title compound.

^{1}H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 3.76 (3H, s), 4.74 (2H, s), 6.12 (1H, d, H=3Hz), 6.29 (1H, d, J=3Hz), 6.51 (1H, br), 6.58 (1H, d, J=9Hz), 6.70 (1H, s), 7.02-7.12 (3H, m), 7.18-7.33 (5H, m's excess), 7.41 (1H, s), 7.95 (1H, s).

LC/MS t=3.82 min [MH^+] 491, 493; [MH^-] 489, 491.

Example 357: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-hydroxy-benzoic acid



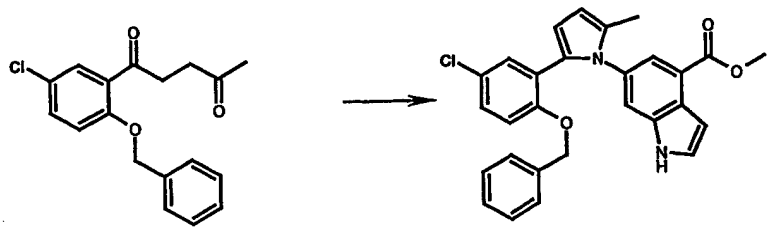
1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (103mg, 0.33mmol), 2-hydroxy-5-amino-benzoic acid (66mg, 0.43mmol) and pTSA (cat) were heated in NMP (1.5mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with Et_2O and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (50%) to give the title compound (56mg)

^{1}H NMR (400MHz, $CDCl_3$) 2.09 (3H, br s), 4.78 (2H, br s), 6.10 (br s), 6.27 (1H, br d, J=2Hz), 6.57 (1H, br d, J=9Hz), 6.79 (1H, br s), 6.93-7.13 (4H, m), 7.16-7.33 (4H, m's excess), 7.55 (1H, br s).

LC/MS t=4.59 min, [MH^+] 434, 436; [MH^-] 432, 434

Example 358: 6-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-1*H*-indole-4-carboxylic acid

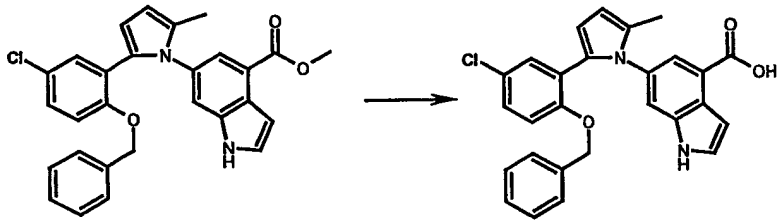
a) 6-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-1*H*-indole-4-carboxylic acid methyl ester



1-[5-chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione, 6-amino-1*H*-indole-4-carboxylic acid methyl ester (prepared from 3,5-dinitro-*o*-toluic acid methyl ester using the Batcho-Leimgruber method as described by Wender *et al*, Proceedings of the National Academy of Sciences of USA, 1986, 83 (12), 4214-4218) (1 equivalent) and pTSA (cat) were heated in NMP (1.5mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (10-20%) to give the title compound.

LC/MS t=4.02 min, [MH^+] 471, 473; [MH^-] 469, 471.

b) 6-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-1H-indole-4-carboxylic acid



6-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-1H-indole-4-carboxylic acid methyl ester, was heated at 100°C in a microwave in a mixture of EtOH (2mL) and 2M NaOH (1mL) for 2 minutes. The mixture was diluted with 2M HCl, and the resultant precipitate was collected by filtration to give the title compound.

LC/MS t=3.77 min, [MH^+] 457, 459; [MH^-] 455, 457.

^{1}H NMR (400MHz, *d*6-DMSO) 2.05 (3H, s), 4.89 (2H, s), 6.05 (1H, d, J=3Hz), 6.24 (1H, d, J=3Hz), 6.93-6.99 (1H, m), 7.06-7.15 (4H, m's excess), 7.22-7.29 (3H, m's excess), 7.36 (1H, s), 7.45 (1H, d, J=2Hz), 7.53 (1H, d, J=3Hz), 11.41 (1H, s), 12.59 (1H, s).

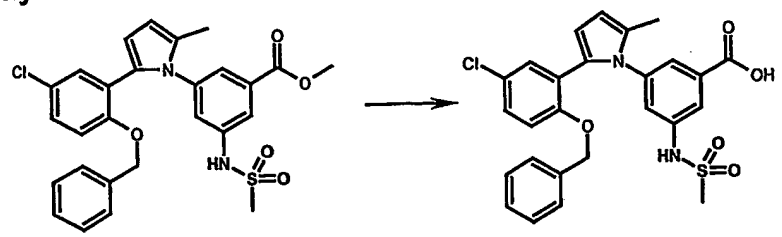
Example 359: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-methanesulfonylamino-benzoic acid

a) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-methanesulfonylamino-benzoic acid methyl ester

Methanesulfonyl chloride (0.1mL, 1.29mmol) was added dropwise to a solution of 3-{2-[5-chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester (104mg, 0.23mmol) and DMAP (cat in DCM-pyridine (1:1, 2mL). The mixture was stirred at room temperature for 2.5hrs then allowed to stand to 6 days then diluted with DCM and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (20-30%) to give the title compound (99mg, 81%).

LC/MS t=3.63 min [MH^+] 445

b) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-methanesulfonylamino-benzoic acid



3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-methanesulfonylamino-benzoic acid methyl ester (99mg) was heated at 100°C in a mixture of EtOH (3mL) and 2M NaOH (1mL) in a microwave for 2 minutes. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated to give the title compound (90mg).

^1H NMR (400MHz, $CDCl_3$) 2.19 (3H, s), 2.68 (3H, s), 4.79 (2H, s), 6.15 (1H, d, H=3Hz), 6.33 (1H, d, J=3Hz), 6.62 (1H, d, J=9Hz), 6.70 (1H, s), 7.01-7.16 (4H, m), 7.23 (1H, d, J=2Hz), 7.25-7.34 (2H, m's excess), 7.60 (1H, s), 7.70 (1H, d, J=5Hz).

LC/MS t=3.73 min [MH^+] 511, 513; [MH] 509, 511.

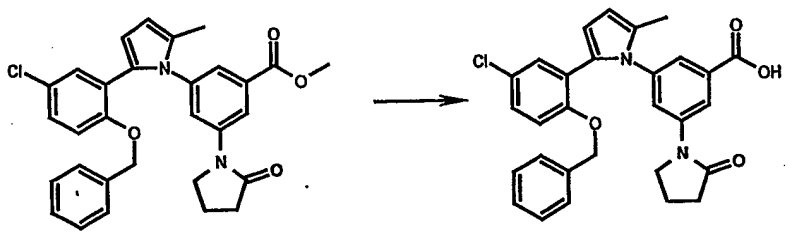
<u>Example 360: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid</u>

a) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester

1-[5-Chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione (114mg), 3-amino-5-(2-oxo-pyrrolidin-1yl)-benzoic acid methyl ester (103mg) and pTSA (cat) were heated in NMP (1.5mL) at 150°C in a microwave for 10 minutes. The mixture was diluted with Et_2O and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (30-50%) to give the title compound (108mg, 65%).

LC/MS t=3.96 min, [MH^+] 515, 517.

b) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid



3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (108mg) was heated at reflux in a mixture of EtOH (2mL) and 2M NaOH (1mL) for 1.5 hours. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated to give the title compound.

^{1}H NMR (400MHz, *d*6-DMSO) 1.94-2.04 (2H, m), 2.44-2.55 (2H, m's excess), 3.55-3.65 (2H, m), 4.81 (2H, s), 6.08 (1H, dd, J=0.5Hz, J=3Hz), 6.24 (1H, d, J=3Hz), 6.85 (1H, d, J=9Hz), 7.05-7.12 (2H, m), 7.16-7.34 (6H, m), 7.56 (1H, t, J=2Hz), 8.20 (1H, t, J=1Hz), 13.00 (1H, br s).

LC/MS t=3.78 min, [MH$^+$] 501, 503; [MH$^-$] 499, 501.

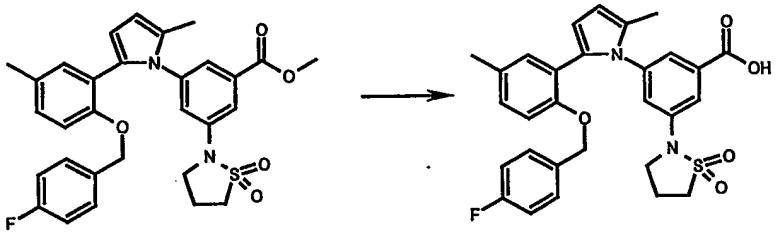
Example 361: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*isothiazolidin*-2-yl)-benzoic acid

a)3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*isothiazolidin*-2-yl)-benzoic acid methyl ester

1-[5-Chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione (110mg), 3-amino-5-(1,1-dioxo-1λ^6-*isothiazolidin*-2-yl)-benzoic acid methyl ester (132mg) and pTSA (cat) were heated in NMP (1.5mL) at 150°C in a microwave for 30 minutes. The mixture was diluted with Et_2O and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (30-50%) to give the title compound (113mg).

LC/MS t=3.93 min [MH$^+$] 551, 553.

b) 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*isothiazolidin*-2-yl)-benzoic acid



3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-(1,1-dioxo-1λ^6-*isothiazolidin*-2-yl)-benzoic acid methyl ester (112mg) was heated at reflux in a mixture of EtOH (2mL) and 2M NaOH (1mL) for 1.5 hours. The mixture was diluted with DCM and 2M HCl and filtered through a hydrophobic frit, fitted with a plug of Na_2SO_4, and evaporated to give the title compound.

^{1}H NMR (400MHz, *d*6-DMSO) 2.30-2.40 (2H, m), 3.48-3.59 (4H, m), 4.84 (2H, s), 6.19 (1H, d, J=3Hz), 6.24 (1H, d, J=3Hz), 6.85 (1H, d, J=9Hz), 7.06 (1H, t, J=2Hz), 7.08-7.35 (8H, m), 7.68-7.72 (1H, m).

LC/MS t=3.73 min, [MH$^+$] 537, 539; [MH$^-$] 535, 537.

Example 362: 3-{2-[5-Chloro-2-(tetrahydro-pyran-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) Toluene-4-sulfonic acid tetrahydro-pyran-4-yl-methyl ester

Tetrahydropyran-4-yl-carboxylic acid (207mg, 1.59mmol) was dissolved in THF (3.2mL). 1M borane-THF (3.2mL) was added and the mixture was stirred at room temperature for 6 hours, after which time water was added. The mixture was extracted twice with EtOAc. The combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in DCM-pyridine (1:1, 3.2mL). Tosyl chloride (327mg, 1.71mmol) was added to

this solution. Stirring was continued overnight, after which time the mixture was diluted with DCM and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (20%), as eluant, to give the title compound (66mg).

Rf 0.49 (50% EtOAc in iso-hexane).

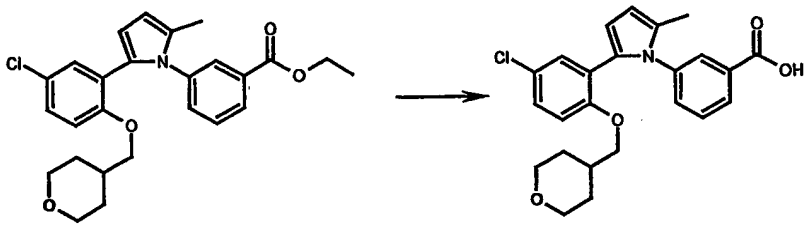
^1H NMR (400MHz, $CDCl_3$) 1.17 (2H, m's excess), 1.51-1.66 (2H, m's excess), 1.86-2.01 (1H, m), 2.47 (3H, s), 3.34 (2H, t, J=12Hz), 3.86 (2H, d, J=6Hz), 3.95-4.00 (2H, m), 7.35 (2H, d, J=8Hz), 7.78 (2H, d, J=8Hz).

b) 3-{2-[5-Chloro-2-(tetrahydro-pyran-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (27mg) was heated in DMF at 60°C with potassium carbonate (25mg) and toluene-4-sulfonic acid tetrahydro-pyran-4-yl-methyl ester (21mg) for 24 hours. The mixture was then diluted with Et_2O and water. The organic phase was separated, dried (Na_2SO_4), filtered and concentrated to give the title compound (27mg).

LC/MS t=3.98 min [MH^+] 454, 456.

c) 3-{2-[5-Chloro-2-(tetrahydro-pyran-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



3-{2-[5-Chloro-2-(tetrahydro-pyran-4-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (27mg) was heated at reflux in a mixture of EtOH (0.6mL) and 2M NaOH (0.3mL) for 1.5 hours. The mixture was diluted with EtOAc and washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated. The residue was purified by MDAP to give the title compound (13mg).

LC/MS t=3.72 min [MH^+] 426, 428; [MH^-] 424, 426.

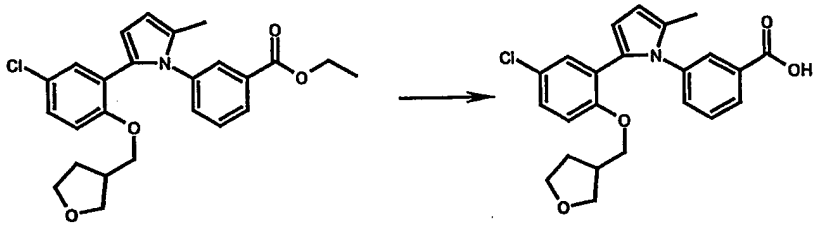
Example 363: 3-{2-[5-Chloro-2-(tetrahydro-furan-3-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Chloro-2-(tetrahydro-furan-3-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

3-{2-[5-Chloro-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (195mg) was heated in DMF (1.2mL) at 60°C with potassium carbonate (166mg) and tetrahydrofurfuryl bromide (172mg) for 24 hours. Further tetrahydrofurfuryl bromide (0.400g) was added and heating continued for 20 hours. The mixture was then diluted with Et_2O and water. The organic phase was separated, dried (Na_2SO_4), filtered and concentrated to give the title compound.

LC/MS t=3.95 min [MH^+] 440, 442.

b) 3-{2-[5-Chloro-2-(tetrahydro-furan-3-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



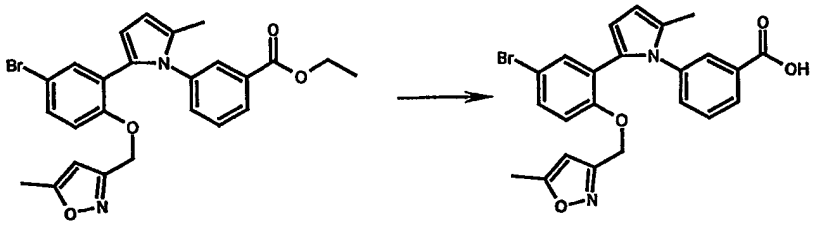
3-{2-[5-Chloro-2-(tetrahydro-furan-3-ylmethoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (110mg) was heated at reflux in a mixture of EtOH (2mL) and 2M NaOH (1mL) for 2 hours. The mixture was diluted with EtOAc and washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated. The residue was purified by MDAP to give the title compound.
LC/MS t=3.68 min [MH^+] 412, 414; [MH^-] 410, 412.

Example 364: 3-{2-[5-Bromo-2-(5-methyl-isoxazol-3-yl-methoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 3-{2-[5-Bromo-2-(5-methyl-isoxazol-3-yl-methoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester

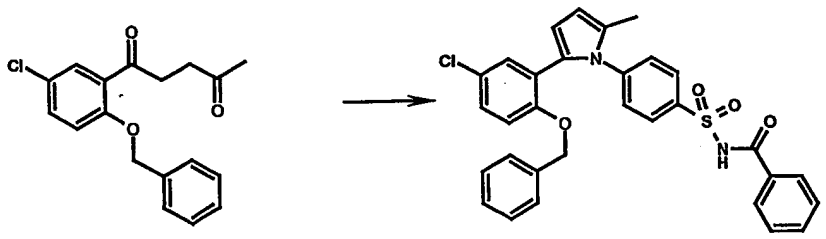
3-{2-[5-Bromo-2-(hydroxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester (0.3mmol) was heated in DMF (1.5mL) at 60°C with potassium carbonate (64mg), 3-(chloromethyl)-5-methyl isoxazole (45mg) and sodium iodide (cat) for 5.5 hours. The mixture was then diluted with Et_2O and water. The organic phase was separated, dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed on silica gel with iso-hexane containing EtOAc (10%), as eluant, to give the title compound.
LC/MS t=4.01 min [MH^+] 495, 497.

b) 3-{2-[5-bromo-2-(5-methyl-isoxazol-3-yl-methoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



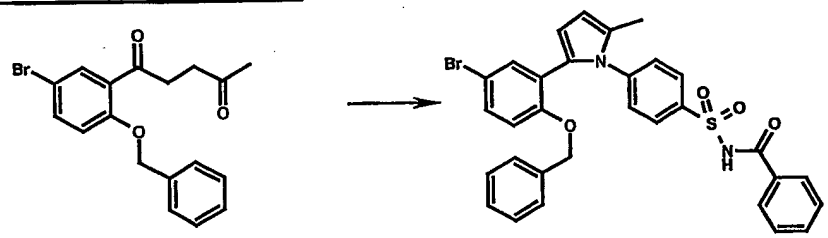
3-{2-[5-Bromo-2-(5-methyl-isoxazol-3-yl-methoxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid ethyl ester was heated, at 100°C in a microwave, in a mixture of EtOH and 2M NaOH for 2 minutes. The mixture was diluted with 2M HCl, and the resultant precipitate was collected by filtration to give the title compound.
LC/MS t=3.77 min [MH^+] 457, 459; [MH^-] 465, 467.

Example 365: 4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-N-(1-phenyl-methanoyl)-benzenesulfonamide.



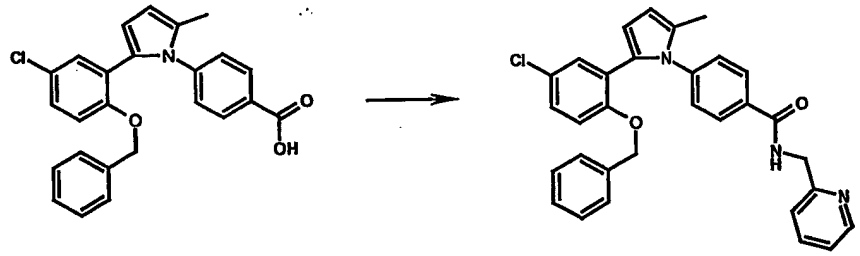
1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (252mg, 0.80mmol), sulfabenzamide (230mg) and pTSA (cat) were heated at reflux in toluene (8mL) for 4 hours. The mixture was diluted with EtOAc and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (30-80%) to give the title compound.
LC/MS t=4.32 min, [MH^+] 557, 559; [MH^-] 555, 557.

Example 366: 4-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-N-(1-phenyl-methanoyl)-benzenesulfonamide.



1-[5-Bromo-2-benzyloxy)-phenyl]-pentane-1,4-dione (263mg, 0.73mmol), sulfabenzamide (210mg) and pTSA (cat) were heated at reflux in toluene (7.3mL) for 3.5 hours. The mixture was diluted with EtOAc and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (30-80%) to give the title compound.
LC/MS t=4.38 min, [MH^+] 601, 603; [MH^-] 599, 601.

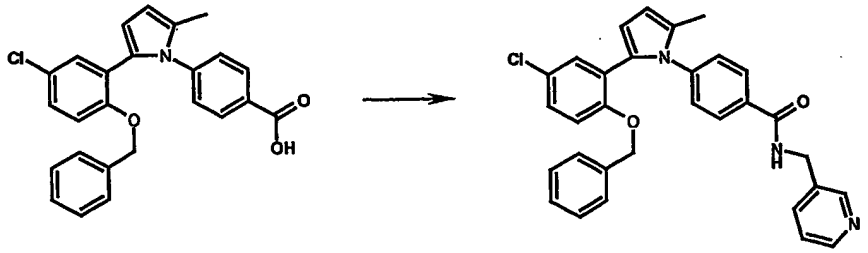
Example 367: 4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-N-(pyridin-2-ylmethyl)-benzamide.



4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (24mg) was dissolved in a mixture of MeCN (0.6mL) and DCM (0.2mL): EDC (15mg) and HOBt (11mg) were added and the mixture stirred for 5 minutes before 2-(aminomethyl)pyridine (12.5µL) was added. The mixture was stirred overnight then diluted with EtOAc and washed sequentially with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with EtOAc to give the title compound.

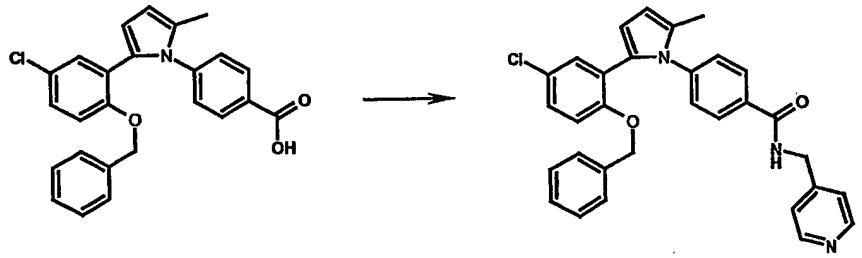
^{1}H NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 4.70 (2H, s), 4.75 (2H, d, J=5Hz), 6.13 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.55 (1H, d, J=9Hz), 6.95-7.18 (5H, m), 7.16-7.47 (5H, m's excess), 7.55-7.80 (4H, m), 8.57 (1H, d, J5Hz).
LC/MS t=3.79 min, [MH^+] 508, 510.

Example 368: 4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-N-(pyridin-3-ylmethyl)-benzamide.



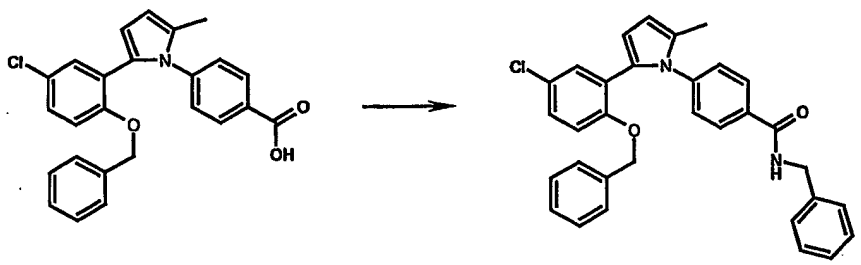
4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (24mg) was dissolved in a mixture of MeCN (0.6mL) and DCM (0.2mL). EDC (15mg) and HOBt (11mg) were added and the mixture stirred for 5 minutes before 3-(aminomethyl)pyridine (12.5µL) was added. The mixture was stirred overnight then diluted with EtOAc and washed sequentially with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified by MDAP to give the title compound.
LC/MS t=3.64 min, [MH^+] 508, 510, [MH^-] 506, 508.

Example 369: 4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-N-(pyridin-4-ylmethyl)-benzamide.



4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (24mg) was dissolved in a mixture of MeCN (0.6mL) and DCM (0.2mL). EDC (15mg) and HOBt (11mg) were added and the mixture stirred for 5 minutes before 4-(aminomethyl)pyridine (12.5µL) was added. The mixture was stirred overnight then diluted with EtOAc and washed sequentially with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified by MDAP to give the title compound.
LC/MS t=3.51 min, [MH^+] 508, 510, [MH^-] 506, 508.

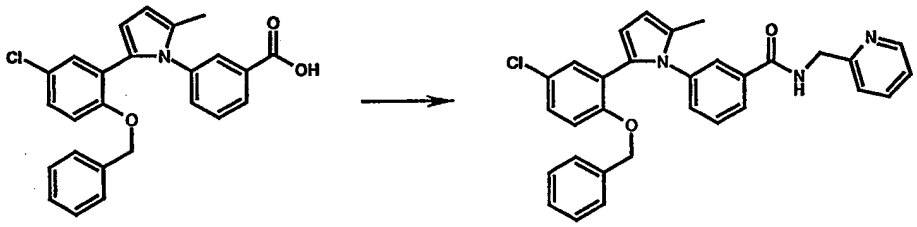
Example 370: 4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-N-(benzyl)-benzamide.



4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (24mg) was dissolved in a mixture of MeCN (0.6mL) and DCM (0.2mL). EDC (15mg) and HOBt (11mg) were added and the mixture stirred for 5 minutes before benzylamine (12.5μL) was added. The mixture was stirred overnight then diluted with EtOAc and washed sequentially with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silca gel with iso-hexane containing EtOAc (10-30%) to give the title compound.

LC/MS t=4.07 min, [MH^+] 507, 509.

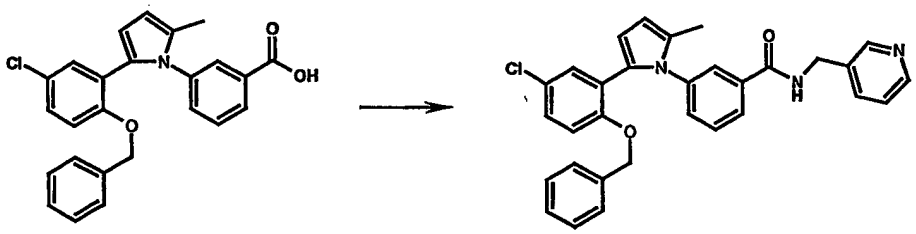
Example 371: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-N-(pyridin-2-ylmethyl)-benzamide.



3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (20mg) was dissolved in DCM (0.5mL). EDC (12mg) and HOBt (9mg) were added and the mixture stirred for 5 minutes before 2-(aminomethyl)pyridine (11μL) was added. The mixture was stirred overnight then diluted with EtOAc and washed sequentially with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with EtOAc to give the title compound.

LC/MS t=3.77 min, [MH^+] 508, 510; [MH^-] 506, 508.

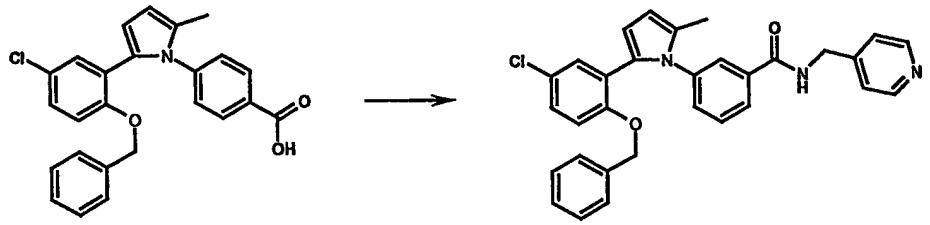
Example 372: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-N-(pyridin-3-ylmethyl)-benzamide.



3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (20mg) was dissolved in DCM (0.5mL). EDC (12mg) and HOBt (9mg) were added and the mixture stirred for 5 minutes before 3-(aminomethyl)pyridine (11μL) was added. The mixture was

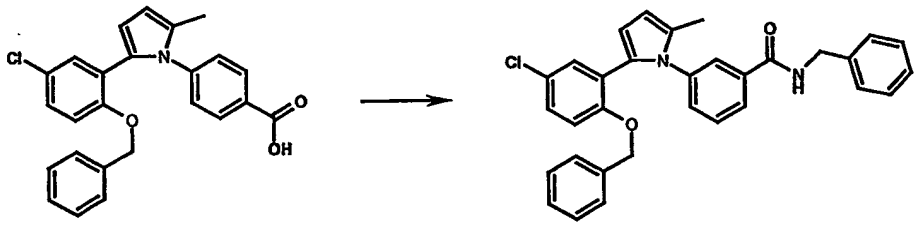
stirred overnight then diluted with EtOAc and washed sequentially with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with EtOAc to give the title compound.
LC/MS t=3.63 min, [MH^+] 508, 510; [MH^-] 506, 508.

Eaxmple 373: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-N-(pyridin-4-ylmethyl)-benzamide.



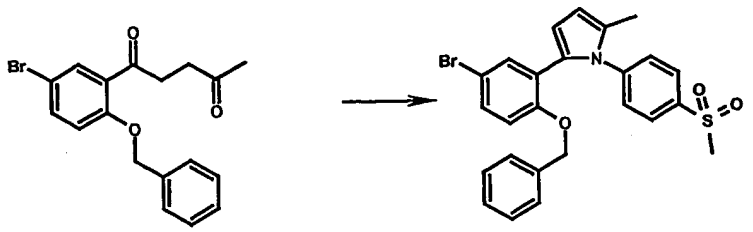
3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (20mg) was dissolved in DCM (0.5mL). EDC (12mg) and HOBt (9mg) were added and the mixture stirred for 5 minutes before 4-(aminomethyl)pyridine (11μL) was added. The mixture was stirred overnight then diluted with EtOAc and washed sequentially with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with EtOAc to give the title compound.
LC/MS t=3.63 min, [MH^+] 508, 510; [MH^-] 506, 508.

Example 374: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-N-(benzyl)-benzamide.



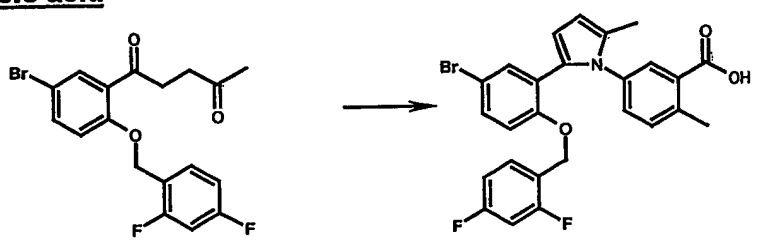
3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid (20mg) was dissolved in DCM (0.5mL). EDC (12mg) and HOBt (9mg) were added and the mixture stirred for 5 minutes before benzylamine (11μL) was added. The mixture was stirred overnight then diluted with EtOAc and washed sequentially with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with EtOAc to give the title compound.
LC/MS t=4.06 min, [MH^+] 507, 509; [MH^-] 505, 507.

Example 375: 4-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-methylsulfonyl benzene.



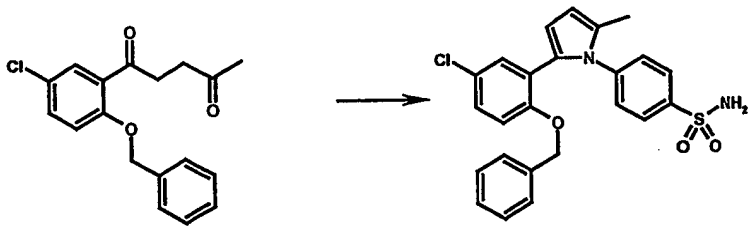
1-[5-Bromo-2-benzyloxy)-phenyl]-pentane-1,4-dione (262mg), 4-(methylsulfonyl)aniline hydrochloride (198mg) and TEA (0.10mL) were heated at reflux in toluene (7.8mL) for 24 hours. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (10-30%) to give the title compound.
LC/MS t=3.86 min, [MH^+] 496, 498.

Example 376: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid



1-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (114mg), 5-amino-2-methyl-benzoic acid (52mg) and pTSA (cat) were heated in NMP (1.5mL) at 150°C for 10 minutes. The mixture was diluted with Et_2O washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated. The residue was purified by MDAP, to give the title compound (79mg).
^1H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 2.62 (3H, s), 4.75 (2H, s), 6.12 (1H, d, J=3Hz), 6.28 (1H, J=3Hz), 6.56 (1H, d, J=9Hz), 6.72–6.82 (2H, m), 6.92-6.99 (1H, m), 7.01 (1H, dd, J=2Hz, J=8Hz), 7.12 (1H, d, J=8Hz), 7.22 (1H, dd, J=2Hz, J=9Hz), 7.38 (1H, d, J=3Hz), 7.74 (1H, d, J=2Hz).
LC/MS t=4.11 min, [MH^+] 512, 514; [MH^-] 510, 512

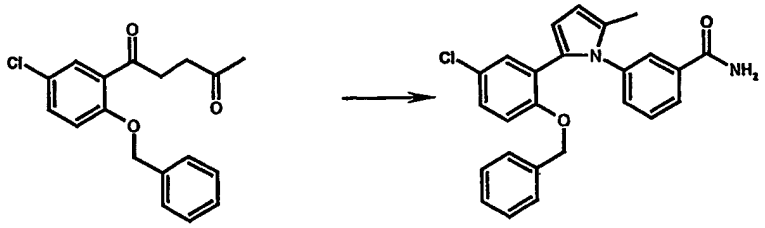
Example 377: 4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzene sulfonamide



1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (508mg, 1.61mmol), sulfanilamide (336mg, 1.95mmol) and pTSA (cat) were heated at relux in toluene (8mL) for 3.5 days. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (20-40%) to give the title compound.

LC/MS t=3.68 min, [MH^+] 453, 455; [MH^-] 451, 453.

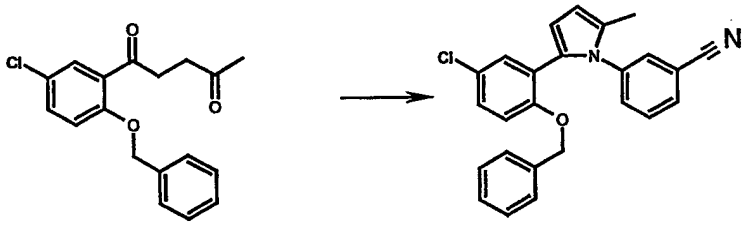
Example 378: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzamide



1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (303mg, 0.96mmol), 3-aminobenzamide (212mg, 1.56mmol) and pTSA (cat) were heated at relux in toluene (5mL) for 2.5 hours. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (30-50%) to give the title compound (293mg, 74%).

LC/MS t=3.61 min, [MH^+] 417, 419.

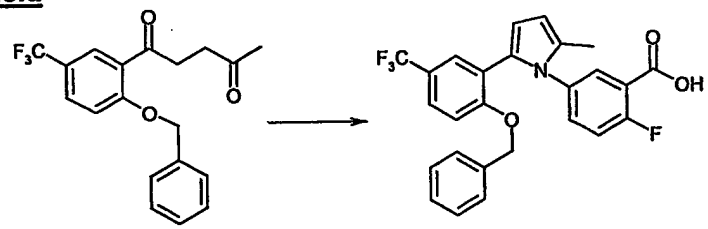
Example 379: 3-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzonitrile



1-[5-Chloro-2-benzyloxy)-phenyl]-pentane-1,4-dione (254mg, 0.80mmol), 3-aminobenzonitrile (212mg, 1.13mmol) and pTSA (cat) were heated at relux in toluene (4mL) for 2.5 hours. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (2-5%) to give the title compound (259mg, 81%).

LC/MS t=3.98 min, [MH^+] 399, 401.

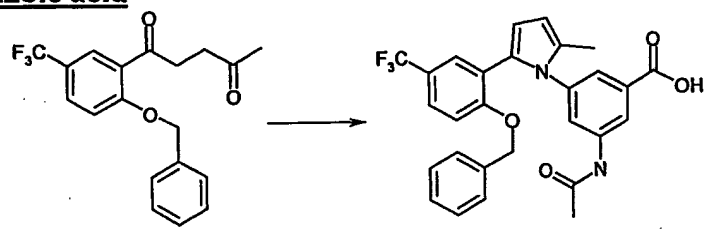
Example 380: 3-{2-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-fluoro-benzoic acid



Procedure as for 3-{2-[5-trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.

^{1}H NMR (400MHz, $CDCl_3$) 2.14 (3H, s), 4.87 (2H, s), 6.13 (1H, d, J=3Hz), 6.34 (1H, d, J=3Hz), 6.76 (1H, d, J=8Hz), 6.98 (1H, t J=9Hz), 7.07-7.14 (3H, m), 7.22-7.41 (4H, m's excess), 7.50 (1H, s), 7.69 (1H, dd, J=6Hz, 3Hz).
LC/MS t=4.01min [MH^+] 470.

Example 381: 3-{2-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-acetylamino-benzoic acid



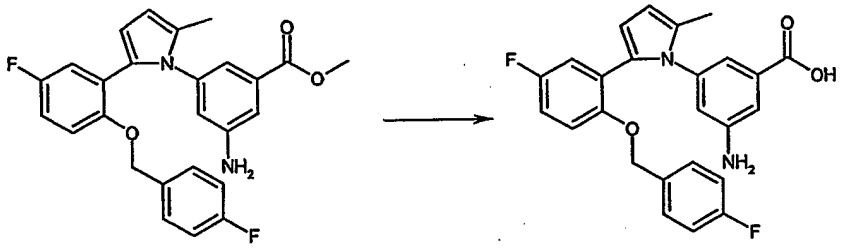
Procedure as for 3-{2-[5-trifluoromethyl-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-chloro-benzoic acid using the appropriate amine, to give the title compound.
^{1}H NMR (400MHz, $CDCl_3$) 2.11 (3H, s), 2.16 (3H, s), 4.87 (2H, s), 5.22 (1H, s), 6.13 (1H, d, J=3Hz), 6.35 (1H, d, J=3Hz), 6.73 (1H, d, J=8Hz), 7.06-7.13 (3H, m), 7.24-7.50 (7H, m), 8.02 (1H, brs).
LC/MS t=3.72min [MH^+] 509.

Example 382: 3-{2-[5-Fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid

a) 3-{2-[5-fluoro-2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid methyl ester

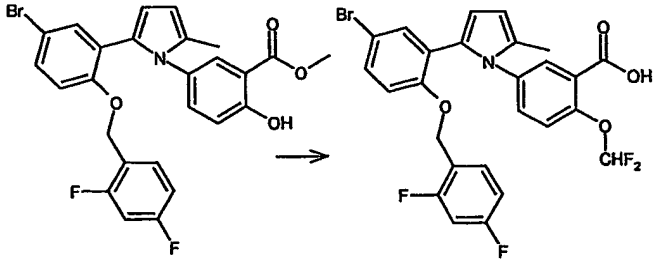
Procedure as for 3-{2-[5-fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid methyl ester.
LC/MS t=3.77 min [MH^+] 449.

b) 3-{2-[5-fluoro-2-(4-Fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-5-amino-benzoic acid



Procedure as for 3-{2-[5-fluoro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-difluoromethoxy-benzoic acid using the appropriate amine.
^{1}H-NMR (400MHz, *d*6-DMSO) 2.09 (3H, s), 4.91 (2H, s), 6.04 (1H, d, J=3Hz), 6.27 (1H, d, J=3Hz), 6.60 (1H, s), 6.79 (1H, dd, J=3Hz, 9Hz), 6.85 (1H, s), 6.88-7.00 (2H, m), 7.15-7.24 (3H, m), 7.26-7.33 (2H, m).
LC/MS t=3.58 min [MH^+] 435

Example 383: 3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl)]-5-methypyrrol-1-yl}-6-difluoromethoxy-benzoic acid.

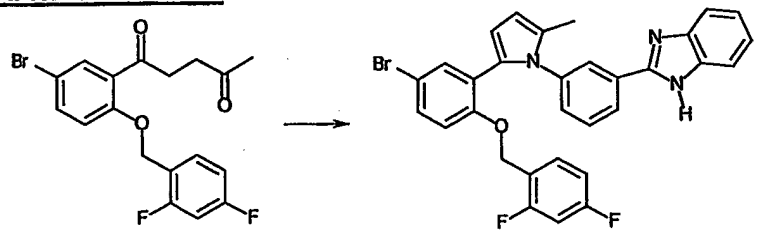


3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methylpyrrol-1-yl}-6-hydroxy-benzoic acid methyl ester (217mg, 0.4mmol) was treated with anhydrous potassium carbonate (100mg, 0.6mmol) and sodium chlorodifluoroacetate (100mg, 7mmol) in dimethylformamide (4.5ml) at room temperature.The reaction mixture was then gradually heated to 100°Cand kept at 100°C for 3 hours. The reaction mixture was cooled, filtered through celite and thoroughly washed with DCM. The filtrate was washed with brine, dried (MgSO4), filtered and evaporated. The residue was purified on a Water's sep-pack (10mg) with Et_2O/iso-hexane, to give the intermediate ester, which was hydrolysed in the same way as 3-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl)]-5-methypyrrol-1-yl}-6-difluoromethoxy-benzoic acid.(65mg, 27%).

^{1}H NMR (400MHz, $CDCl_3$) 2.12 (3H, s), 4.73 (2H, s), 6.12 (1H, d, J=3Hz), 6.28 (1H, d, J=3Hz), 6.39-6.87 (4H, m), 6.99-7.15 (3H, m), 7.23-7.29 (1H, m excess), 7.38 (1H, d, J=2Hz), 7.67 (1H, d, J=2Hz).

LC/MS t=4.08 min [MH^+] 566

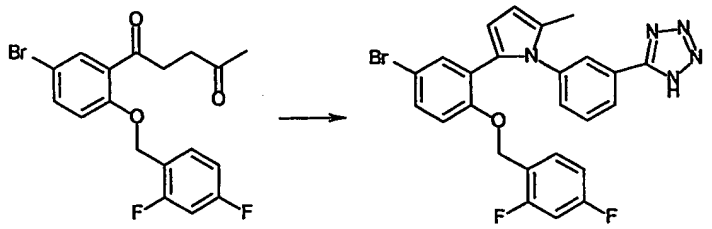
Example 384: 2-(3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-phenyl)-1*H*-benzoimidazole



1-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (100mg, 0.25mmol), 3-(1H-benzoimidazol-2-yl)-phenylamine (63mg, 0.3mmol) {Brana *et al*, *J. Het. Chem.*, 1990, 27(5), 1177-80}, and p-toluenesulfonic acid (10mg) were heated in toluene (1ml) at reflux for 19 hours. Upon cooling, the mixture was diluted with EtOAc (3ml) and washed with 2M HCl (2ml), saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified by MDAP, to give the title compound (77mg, 53%).

LC/MS t=4.04 min [MH^+] 570/572.

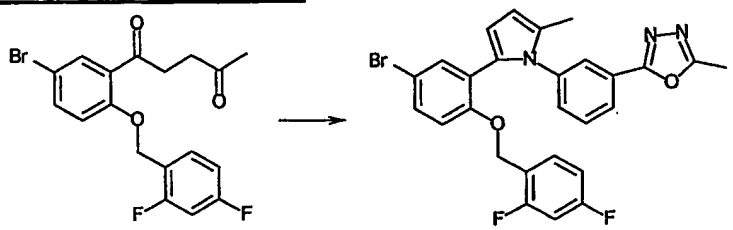
Example 385: 5-(3-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-phenyl)-1*H*-tetrazole



Preparation as for 2-(3-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-phenyl)-1*H*-benzoimidazole using the appropriate amine to give the title compound (80mg, 60%).

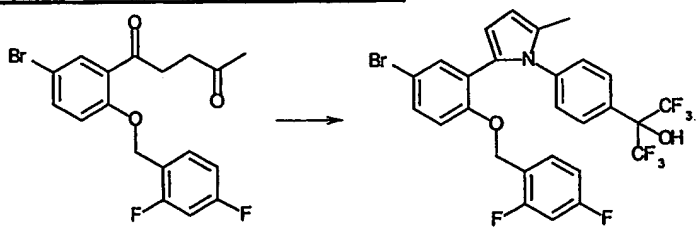
^{1}H NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 4.74 (2H, s), 6.14 (1H, d, J=2Hz), 6.31 (1H, d, J=2Hz), 6.57 (1H, d, J=10Hz), 6.72 (2H, m), 7.01 (1H, t, J=8Hz), 7.11 (1H, bdd, J=8Hz), 7.22 (1H, dd, J=8Hz), 7.40 (2H, m), 7.73 (1H, bs), 7.99 (1H, bd, J=8Hz).
LC/MS t=4.38 min [MH^+] 522/524.

Example 386: 2-(3-{2-[5-Bromo-2-(2,4difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-phenyl)-5-methyl-[1,3,4]oxadiazole



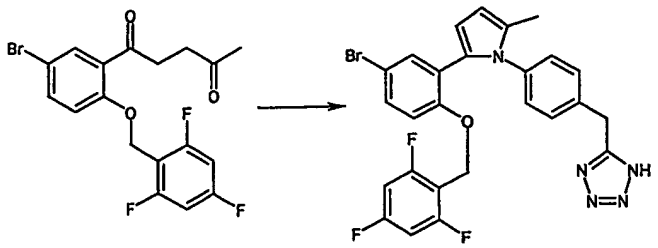
Preparation as for 2-(3-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-phenyl)-1*H*-benzoimidazole using the appropriate amine (Hoefle *et al*, US4824843) (31mg, 22%).
LC/MS t= 3.99 min [MH^+] 536/538.

Example 387: 2-(4-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1yl}-phenyl)-1,1,1,3,3,3-hexafluoro-propan-2-ol



Preparation as for 2-(3-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-phenyl)-1*H*-benzoimidazole using the appropriate amine (5mg, 3%).
^{1}H NMR (400MHz, $CDCl_3$) 2.20 (3H, s), 4.61 (2H, s), 6.13 (1H, d, J=3Hz), 6.33 (1H, d, J=4Hz), 6.55 (1H, d, J=8Hz), 6.76-6.86 (2H, m), 7.03-7.06 (2H, m), 7.08-7.16 (1H, m), 7.22 (1H, dd, J=2, 8Hz), 7.30 (1H, d, J=2Hz).7.59 (2H, d, J=8Hz).
LC/MS t= 4.26 min [MH^+] 620/622.

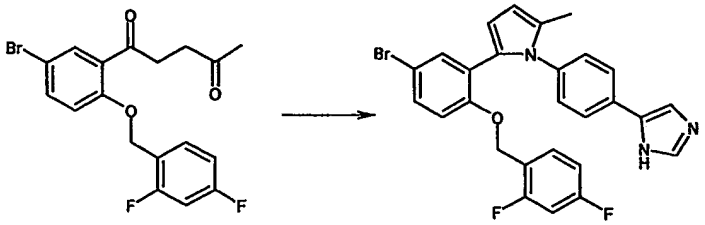
Example 388: 5-(4-{2-[5-Bromo-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzyl)-1*H*- tetrazole



Procedure as for 3-{2-[5-bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-acetylamino-benzoic acid methyl ester using the appropriate amine (Kees *et al*, *J. Med. Chem*, 1992, 35(5), 944-53), however further purification was achieved using the MDAP.

^{1}H-NMR (400MHz, $CDCl_3$) 2.13 (3H, s), 4.34 (2H, s), 4.78 (2H, s), 6.06 (1H, d, J=3Hz), 6.29 (1H, d, J=3Hz), 6.67 (2H, t, J=8Hz), 6.73 (1H, d, J=9Hz), 6.99 (2H, d, J=9Hz), 7.13 (1H, d, J=2Hz), 7.17 (2H, d, J=9Hz), 7.22 (1H, dd, J=3Hz, 9Hz).
LC/MS t=3.68 min [MH^+] 554/556.

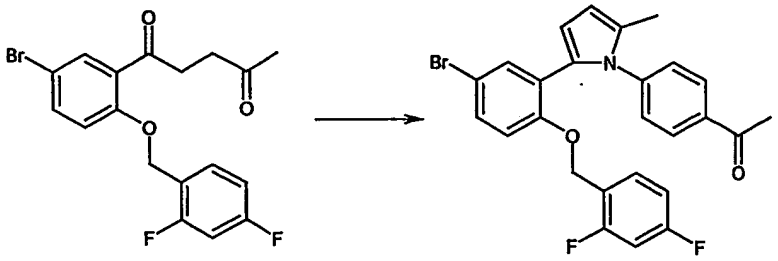
Example 389: 5-(4-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-phenyl)-1*H*-imidazole



Procedure as for 4-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzamide using the appropriate amine to give title compound.

LC/MS t=3.38 min [MH^+] 519/521.

Example 390: 1-(4-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-phenyl)-ethanone



1-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-pentane-1,4-dione (0.10g, 0.25mmol), 4-ethynyl-phenylamine (0.035g, 0.3mmol) and *p*-TSA (0.009g, 0.05mmol) were refluxed in toluene (1.5ml) for 18 hours under a nitrogen atmosphere. The solvent was removed *in vacuo* and the resultant residue purified by MDA to give the title compound.

^{1}H-NMR (400MHz, $CDCl_3$) 2.17 (3H, s), 2.58 (3H, s), 4.70 (2H, s), 6.13 (1H, d, J=3Hz), 6.30 (1H, d, J=3Hz), 6.56 (1H, d, J=9Hz), 6.75-6.83 (2H, m), 6.94 (1H, q, J=7Hz), 7.00-7.04 (2H, m), 7.23 (1H, dd, J=3Hz, 9Hz), 7.37 (1H, d, J=3Hz), 7.79-7.84 (2H, m).
LC/MS t=4.08 min [MH^+] 498/500.

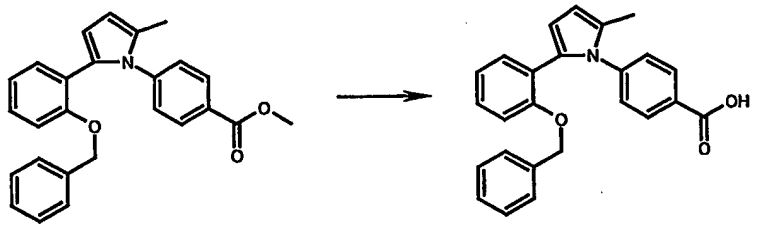
Example 391: 4-{2-[2-(Benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 4-{2-[2-(Benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid methyl ester

1-[2-(benzyloxy)-phenyl]-pentane-1,4-dione (540mg), 4-amino-benzoic acid methyl ester (355mg) and pTSA (cat) were heated at reflux in toluene (20mL) for 5 hours. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc (3-5%) to give the title compound (684mg)

Rf 0.61 (30% EtOAc in hexanes).

b) 4-{2-[2-(Benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



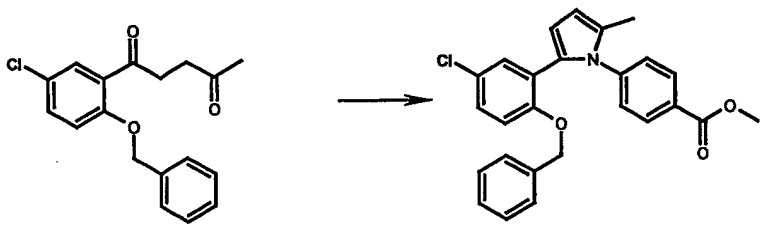
3-{2-[2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid methyl ester (214mg) was heated in a reacti-vial at 85°C in a mixture of DMF (4.0mL) and 2M NaOH (2.0mL) for 24 hours. The mixture was diluted with EtOAc and washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated. The residue was chromatographed on silica gel, with iso-hexane-EtOAc-AcOH (90:10:2 to 70:30:2) as eluant, to give the title compound (140mg).

Rf 0.35 iso-hexane-EtOAc-AcOH (70:30:2)

LC/MS t=3.57 min [MH^+] 384, [MH$^-$] 382.

Example 392: 4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

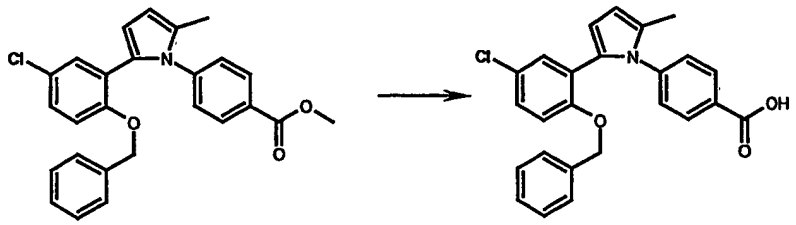
a) 4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid methyl ester



1-[5-Chloro-2-(benzyloxy)-phenyl]-pentane-1,4-dione (1.013g), 4-amino-benzoic acid methyl ester (616mg) and pTSA (cat) were heated at reflux in toluene (34mL) overnight. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel with iso-hexane containing EtOAc to give the title compound (815mg)

Rf 0.74 (30% EtOAc in iso-hexane)

b) 4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



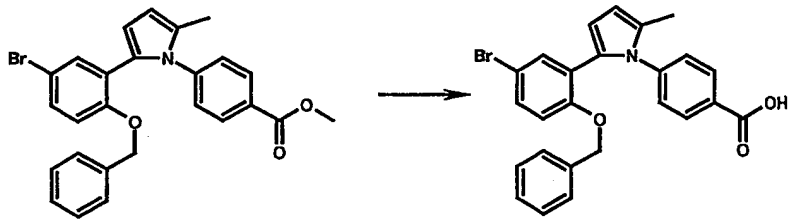
4-{2-[5-Chloro-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid methyl ester (152mg) was heated at reflux in a mixture of EtOH (3.0mL) and 2M NaOH (1.0mL) overnight. The mixture was diluted with EtOAc and washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound.
LC/MS t=3.73 min, [MH^+] 418; [MH^-] 416, 418.

Example 393: 4-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid

a) 4-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid methyl ester

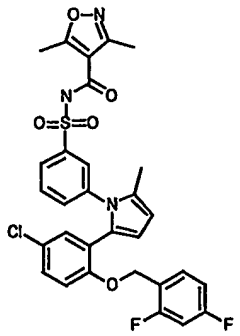
1-[5-Bromo-2-(benzyloxy)-phenyl]-pentane-1,4-dione (1.020g), 4-amino-benzoic acid methyl ester (581mg) and pTSA (cat) were heated at reflux in toluene (30mL) overnight. The mixture was diluted with EtOAc and washed sequentially with 2M HCl and saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel, with iso-hexane containing EtOAc (5%) as eluant, to give the title compound (757mg)
^1H NMR (400MHz, $CDCl_3$) 2.15 (3H, s), 3.91 (3H, s), 4.68 (2H, s), 6.16 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.50 (1H, d, J=9Hz), 6.97-7.06 (4H, m), 7.19 (1H, dd, J=3Hz, J=9Hz), 7.23-7.34 (3H, m's excess), 7.39 (1H, d, J=2Hz), 7.88 (2H, d, J=8Hz).

b) 4-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid



4-{2-[5-Bromo-2-(benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-benzoic acid methyl ester (152mg) was heated at reflux in a mixture of EtOH (3.0mL) and 2M NaOH (1.5mL) for 3 hours. The mixture was diluted with EtOAc and washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound.
LC/MS t=4.01 min, [MH^+] 462; [MH^-] 460.

Example 394: 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-[1-(3,5-dimethyl-isoxazol-4-yl)-methanoyl]-benzenesulfonamide



Prepared in the same way as 3-{2-[5-chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-*N*-[1-phenyl-methanoyl]-benzenesulfonamide.
LC/MS t=4.51 min, [MH^+] 612, 614; [MH^-] 610, 612.

Microwave

Emrys Optimiser and Smith Creator (300 Watt) supplied by Personal Chemistry.

Mass Directed Auto-Purification System

Hardware

Waters 600 gradient pump
Waters 2700 sample manager
Waters Reagent manager
Waters 996 photodiode array dectector
Micromass ZQ mass spectrometer
Gilson 202 fraction collector
Gilson Aspec waste collector

Software

Micromass Masslynx version 3.5

Column

The column used is a Supelcosil™ ABZ+PLUS, the dimensions of which are 21.2mm x 100mm. The stationary phase particle size is 5µm.

Solvents

A : Aqueous solvent = Water + 0.1% Formic Acid
B : Organic solvent = Acetonitrile + 0.1% Formic Acid
Make up solvent = Methanol : Water 80:20 + 2mMol Ammonium Acetate
Needle rinse solvent = Methanol : Water : Dimethylsulfoxide 80:10:10

Methods

There are five methods used depending on the analytical retention time of the compound of interest. They all have a 15-minute runtime, which comprises of a 10-minute gradient followed by a 5 minute column flush and re-equilibration step.
MDP 1.5-2.2 = 0-20% B
MDP 2.0-2.8 = 0-30% B
MDP 2.5-3.0 = 15-55% B
MDP 2.8-4.0 = 30-85% B

MDP 3.8-5.5 = 50-99% B

Flow rate

All of the above methods have a flow rate of 20ml/mins

LCMS Systems

Hardware

Agilent 1100 gradient pump

Agilent 1100 Autosampler

Agilent 1100 PDA Dectector

Agilent 1100 Degasser

Micromass ZQ mass spectrometer

PL-ELS 1000

Software

Micromass Masslynx versions 3.5/4.0

Column

The column used is a Supelcosil™ ABZ+PLUS, the dimensions of which are 4.6mm x 33mm. The stationary phase particle size is 3µm.

Solvents

A : Aqueous solvent = 10mMol Ammonium Acetate + 0.1% Formic Acid

B : Organic solvent = 95 %Acetonitrile + 0.05% Formic Acid

Method

The generic method used has 5.5 minute runtime, which comprises of a 4.7-minute gradient (0-100% B) followed by a 0.6 minute column flush and 0.2 minute re-equilibration step.

Flow rate

The above method has a flow rate of 3ml/mins

NMR

Hardware

Bruker 400MHz Ultrashield™

Bruker B-ACS60 Autosampler

Bruker Advance 400 Console

Software

User interface – NMR Kiosk

Controlling software – XWin NMR version 3.0

ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

The compounds of formula (I) can be tested using the following assays to demonstrate their prostanoid antagonist or agonist activity in vitro and in vivo and their selectivity. The prostaglandin receptors investigated are DP, EP_1, EP_2, EP_3, EP_4, FP, IP and TP.

The ability of compounds to antagonise EP_1 & EP_3 receptors may be demonstrated using a functional calcium mobilisation assay. Briefly, the antagonist properties of compounds are assessed by their ability to inhibit the mobilisation of intracellular calcium ($[Ca^{2+}]_i$) in response to activation of EP_1 or EP_3 receptors by the natural agonist hormone prostaglandin E_2 (PGE_2). Increasing concentrations of antagonist reduce the amount of calcium that a given concentration of PGE_2 can mobilise. The net effect is to displace the PGE_2 concentration-effect curve to higher concentrations of PGE_2. The amount of calcium produced is assessed using a calcium-sensitive fluorescent dye such as Fluo-3, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR). Increasing amounts of $[Ca^{2+}]_i$ produced by receptor activation increase the amount of fluorescence produced by the dye and give rise to an increasing signal. The signal may be detected using the FLIPR instrument and the data generated may be analysed with suitable curve-fitting software.

The human EP_1 or EP_3 calcium mobilisation assay (hereafter referred to as 'the calcium assay') utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing either EP_1 or EP_3 cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin and 10□g/ml puromycin.

For assay, cells are harvested using a proprietary reagent that dislodges cells such as Versene. Cells are re-suspended in a suitable quantity of fresh culture media for introduction into a 384-well plate. Following incubation for 24 hours at 37°C the culture media is replaced with a medium containing fluo-3 and the detergent pluronic acid, and a further incubation takes place. Concentrations of compounds are then added to the plate in order to construct concentration-effect curves. This may be performed on the FLIPR in order to assess the agonist properties of the compounds. Concentrations of PGE_2 are then added to the plate in order to assess the antagonist properties of the compounds.

The data so generated may be analysed by means of a computerised curve-fitting routine. The concentration of compound that elicits a half-maximal inhibition of the calcium mobilisation induced by PGE_2 (pIC_{50}) may then be estimated.

By application of this technique, compounds of the examples had an antagonist pIC_{50} value of between 7.0 and 9.5 at EP_1 receptors and pIC50 value of < 6.0 at EP_3 receptors. Preferred compounds have an antagonist pIC_{50} value of greater than 8.0 at EP_1 receptors.

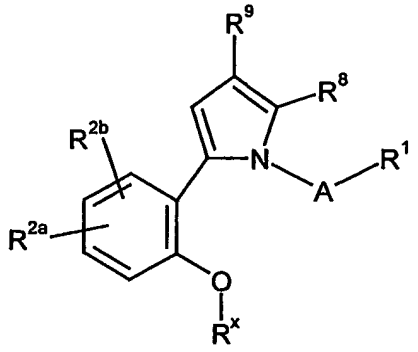
No toxicological effects are indicated/expected when a compound (of the invention) is administered in the above mentioned dosage range.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent

application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

CLAIMS

1. A compound of formula (I):



(I)

wherein:

A represents an optionally substituted aryl group, or an optionally substituted 5- or 6-membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;

R^1 represents CO_2H, CN, $CONR^5R^6$, CH_2CO_2H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO_2alkyl, $SO_2NR^5R^6$, $NR^5CONR^5R^6$, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;

R^{2a} and R^{2b} independently represents hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, CN, SO_2alkyl, SR^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;

R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms may optionally be replaced by a group independently selected from NR^4, O and SO_n, wherein n is 0, 1 or 2: or R^x may be optionally substituted CQ_2-heterocyclyl, optionally substituted CQ_2-bicyclic heterocyclyl or optionally substituted CQ_2-aryl;

R^4 represents hydrogen or an optionally substituted alkyl;

R^5 represents hydrogen or an optionally substituted alkyl;

R^6 represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted SO_2heteroaryl, CN, optionally substituted CQ_2aryl, optionally substituted CQ_2heteroaryl or COR^7;

R^7 represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;

R^8 represents hydrogen, CF_3, or alkyl;

R^9 represents hydrogen, CF_3 or alkyl;

Q is independently selected from hydrogen and CH_3;

wherein when A is a 6-membered ring the R^1 substituent and pyrrole ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring

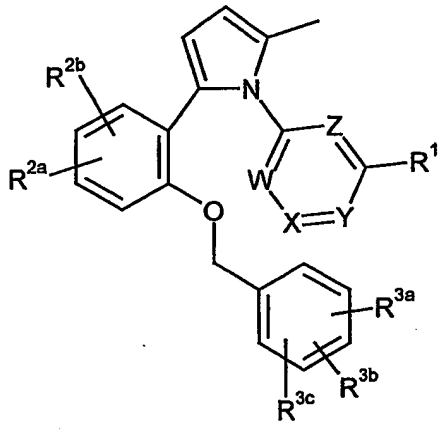
or bicyclic heterocyclyl group the R^1 substituent and pyrrole ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;
or a derivative thereof.

2. A compound according to claim 1 wherein A is selected from phenyl, naphthyl, indolyl, pyridyl, pyridazinyl, pyrazinyl or pyrimidinyl, all of which may be optionally substituted.

3. A compound according to claim 1 or claim 2 wherein R^1 represents CO_2H, CN, $CONR^4R^5$, optionally substituted $CONR^5SO_2$aryl, optionally substituted $CONR^5SO_2$heteroaryl, optionally substituted $CONR^5$aryl, optionally substituted $CONR^5$heteroaryl, $CONR^5SO_2C_{1-6}$alkyl, optionally substituted $CONR^5SO_2$heteroaryl, optionally substituted $CONR^5CQ_2$aryl, optionally substituted $CONR^5CQ_2$heteroaryl, optionally substituted C_{1-6}alkyl, SO_2C_{1-6}alkyl, $SO_2NR^4R^5$, optionally substituted SO_2NR^5COaryl, optionally substituted SO_2NR^5COheteroaryl, $SO_2NR^5COC_{1-6}$alkyl, optionally substituted $SO_2NR^5CQ_2$aryl, optionally substituted $SO_2NR^5CQ_2$heteroaryl; COC_{1-6}alkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycyl, or optionally substituted heterocyclyl; wherein R^4 and R^5 are each selected from hydrogen and C_{1-4}alkyl, and Q is selected from hydrogen and CH_3.

4. A compound according to any one of claims 1 to 3 wherein A is a six membered ring and R^1 substituent is attached to the group A in the 3- or 4-position relative to the bond attaching A to the pyrrole ring.

5. A compound according to any one of claims 1 to 4 which is a compound of formula (Ia):



(Ia)

wherein:
R^1 is CO_2H;
R^{2a} and R^{2b} are independently selected from hydrogen, halo, phenyl, optionally substituted C_{1-6}alkyl e.g. C_{1-4}alkyl and CF_3, CN, SC_{1-6}alkyl, or SO_2C_{1-6}alkyl;

R^{3a}, R^{3b}, and R^{3c} are independently selected from hydrogen, halo, optionally substituted OC_{1-6}alkyl, phenyl or optionally substituted C_{1-6}alkyl;
W, X, Y and Z each represents CR^{12} or N wherein at least two of W, X, Y or Z is CR^{12}; and when each of W, X, Y, and Z is CR^{12} then each R^{12} is independently selected from hydrogen, halogen, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, NR^4R^5, NR^5COC_{1-6}alkyl, $NR^5SO_2C_{1-6}$alkyl, OR^5, C_{1-6}alkyl, SO_2C_{1-6}alkyl, $NR^5COCH_2OC_{1-6}$alkyl, NR^5COCH_2heterocyclyl wherein R^4 and R^5 are each independently selected from hydrogen and C_{1-4}alkyl; and $NR^{10}R^{11}$ wherein R^{10} and R^{11} together with the nitrogen atom to which they are attached form an optionally substituted 5- or 6-membered aliphatic heterocyclic ring wherein one of the ring carbons may be optionally replaced by another heteroatom selected from O and SO_n wherein n is 0, 1 or 2., and when at least one of W, X, Y and Z represents N then each R^{12} is selected from hydrogen and NH_2;
or a derivative thereof.

6. A compound selected from the compound of Examples 11, 33, 41, 46, 49, 55, 60, 72, 76, 85, 88, 103, 106, 112, 122, 125, 150, 155, 157, 175, 176, 180, 183, 188, 191, 200, 207, 209, 211, 222, 225, 234, 235, 236, 237, 239, 240, 241, 245, 250, 254, 261, 262, 278, 283, 295, 306, 314, 316, 332, 338, 348, 353, 358, 356, 367, 376, 383, 385, 387, 388 and 392; and pharmaceutically acceptable derivatives thereof.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof together with a pharmaceutical carrier and/or excipient.

8. A compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for use as an active therapeutic substance.

9. A compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

10. A method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE_2 at EP_1 receptors which comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof.

11. A method of treating a human or animal subject suffering from a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof.

12. A method of treating a human or animal subject suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof.

13. Use of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

14. Use of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder.

15. Use of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as inflammatory pain, neuropathic pain or visceral pain.

16. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, according to claim 1, substantially as hereinbefore described with reference to any one of the Examples.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D207/32 C07D401/04 C07D413/12 C07D401/12 C07D403/12
C07D417/10 C07D401/10 C07D409/12 C07D403/04 C07D405/12
C07D403/10 C07D413/10 A61K31/402 A61K31/4025 A61P13/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 25896 A (SEARLE & CO ;YU YI (US); KHANNA ISH K (US); WEIER RICHARD M (US)) 18 June 1998 (1998-06-18) page 1 -page 4 examples 1,6,25 claims 28,30 ---	1,7
Y	EP 0 799 823 A (SANKYO CO) 8 October 1997 (1997-10-08) example 123; table 13 tables 1,2 page 1 claims 17,18 --- -/--	1,7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
17 September 2003	29/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seitner, I

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P19/08 A61P25/28 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 19814 A (MERCK FROSST CANADA INC ;RUEL REJEAN (CA); LABELLE MARC (CA); LACO) 22 March 2001 (2001-03-22) cited in the application example 2 claims 12-24	1,7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Seitner, I

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/EP 03/05790

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9825896 A	18-06-1998	AU 5377698 A	03-07-1998
		EP 0946507 A1	06-10-1999
		WO 9825896 A1	18-06-1998
		US 5935990 A	10-08-1999
EP 0799823 A	08-10-1997	AU 710380 B2	16-09-1999
		AU 1665397 A	09-10-1997
		CA 2201812 A1	05-10-1997
		CN 1168372 A	24-12-1997
		CZ 9701035 A3	15-10-1997
		EP 0799823 A1	08-10-1997
		HU 9700709 A2	28-05-1999
		JP 3034819 B2	17-04-2000
		JP 9323971 A	16-12-1997
		NO 971564 A	06-10-1997
		NZ 314508 A	29-06-1999
		RU 2125044 C1	20-01-1999
		TW 409122 B	21-10-2000
		US 5908858 A	01-06-1999
		ZA 9702846 A	04-11-1997
WO 0119814 A	22-03-2001	AU 7264200 A	17-04-2001
		WO 0119814 A2	22-03-2001
		CA 2384783 A1	22-03-2001
		EP 1216238 A2	26-06-2002
		JP 2003509419 T	11-03-2003
		US 6369084 B1	09-04-2002